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MALIGNANT DISEASE IN INFANCY AND CHILDHOOD*

BY

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Prophylactic paediatrics, or child health, has made great advances during recent years. The considerable extensions in child health programmes, together with the advent of the sulphonamides and the antibiotics, have caused a marked decline in the infant mortality rate and in the death rate throughout childhood generally. As a result, malignant disease has assumed an increased prominence as a cause of death in children and now ranks higher than some of the commoner infectious diseases occurring in childhood.

Incidence of Malignant Tumours in Childhood

There is no evidence of any increased incidence of malignancy, except of the leukaemias which have certainly become more common. Deaths from leukaemia in children under 14 years, according to the Registrar-General's reports, were 107 in 1940, 209 in 1942, and 235 in 1945. In Manchester, Wilkinson (1948) has found a considerable increase in the past three years, the number now being seen averaging 10 per year compared with 0·7 per year for the preceding fourteen years. These figures confirm the strong clinical impression felt by most paediatricians that more cases of leukaemia are now being seen.

The following figures show the position occupied by malignant tumours (including leukaemia and Hodgkin's disease) as a cause of death in New York, U.S.A., compared with some of the common infectious fevers. They are for the three-year period 1942-44 for children under 14 years of age, and are modified from the Registry of the Memorial Cancer Centre, New York:

Tumours, 392.
Tuberculosis, 291.
Cerebrospinal meningitis, 150.
Whooping-cough, 134.
Anterior poliomyelitis, 86.
Congenital syphilis, 55.
Measles, 35.

For comparison, the position of malignant tumours as a cause of death in children of the same age-groups in England and Wales, for the five-year period 1938-42, is shown. These are compiled from the Registrar-General's reports:

Tuberculosis, 12,052.
Whooping-cough, 6,238.
Tumours, 4,479.
Cerebrospinal meningitis, 3,879.

It is perhaps not widely enough appreciated what a large percentage of malignant tumours appear during the first five years of life; many, indeed, occur during the first three years. There is some practical significance in this fact, for at this period of life the greatest number of curable growths occur.

The American figures from the Mortality Statistics for 1939-43 and the British figures from the Registrar-General's reports for 1938-42, are given in table 1.

TABLE 1

MORTALITY FROM MALIGNANT TUMOURS IN CHILDHOOD

Age-group	England and Wales	U.S.A.
Birth-4 years	1,942	5,525
5–9 years	1,371	3,150
10–14 years	1,116	2,871

Although, in the main, malignant tumours in childhood occur in sites different from those in adults, carcinoma of the stomach, rectum, uterus, and prostate, for example, being very rare, yet growths in almost every organ have been reported. Many of the childhood tumours, however, are peculiar to this age-period and are not seen in later life. The relative frequency with which the different organs or systems are affected shows a remarkable consistency, and has done so for a number of years and in a number of different countries (table 2).

In confirmation of the early age-incidence mentioned previously, it is worth noting that 50 per cent. of the cases at the Royal Manchester Children's Hospital, 60 per cent. of those at the Birmingham Children's Hospital, and 80 per cent. at the Hospital for Sick Children, Great Ormond Street, London, were under 5 years of age.

Helmholz (1931) recorded that 80 per cent. of his series of intracranial tumours and 67 per cent. of the cases with kidney tumours were also under 5 years of age. His material consisted of 750 cases seen in the paediatric department of the Mayo Clinic over the ten-year period from 1921 to 1930.

* A paper read to the Section of Child Health, British Medical Association Annual Meeting, Cambridge, on Friday, July 2, 1948.

1

TABLE 2

FINDINGS OF VARIOUS OBSERVERS AND AT DIFFERENT HOSPITALS SINCE DUZAN'S FIRST CONTRIBUTION TO THE SUBJECT IN 1876

Source of information	Site of tumour in order of frequency			
	1	2	3	4
Duzan, 1876	Eye	Kidney	Testis	—
Steffen, 1905	Kidney	Eye	Intracranial	Bone
Helmholtz, 1931	Intracranial	Leukaemia	Bone	Kidney
Williams, 1946	Bone	Intracranial	Eye	Kidney
Dargeon, 1947	Bone	Kidney	Eye	Leukaemia
Children's Hospital, Birmingham, 1937 and 1947	Leukaemia	Intracranial	Kidney	—
Royal Manchester Children's Hospital, 1943-1947	Leukaemia	Intracranial	Kidney	—
Children's Hospital, Great Ormond Street, 1947	Leukaemia	Intracranial	Kidney	—
Christie Hospital, Manchester, 1941-1945 ..	Intracranial	Leukaemia	Eye	Kidney
Steiner, 1947	Leukaemia	Intracranial	Kidney	—

(Hodgkin's disease is included with leukaemia.)

That malignant disease in childhood generally is not a big problem numerically, may be judged from the figures shown in table 3.

As will be seen, between 0·25 per cent. and 0·5 per cent. of the admissions to a children's hospital may be expected to be malignant tumours; in a cancer institution between 1 per cent. and 2 per cent. of the total number of cases occur in children. Steiner (1947) reported that 2·49 per cent. of all deaths in the twenty-five-year period 1921-45 in the Children's Memorial Hospital, Chicago, were due to malignant disease, and that this was the cause of death in 4·14 per cent. of all autopsies performed at that hospital.

The foregoing figures suggest that it is unlikely that any one practitioner will see sufficient cases to keep the possibility of malignant disease constantly in the forefront of his mind when dealing with infants and children.

If it be remembered that the four commonest sites are as follows: (1) blood, (2) brain, (3) eye, and (4) kidney, and if the early signs and symptoms of these tumours are kept in mind, this would go some way towards ensuring earlier diagnosis and consequent improved prognosis as a result of the more prompt treatment which could be instituted. Particularly is this so as, with the exception of leukaemia, the tumours are capable of being cured in a great many cases.

Earlier diagnosis and treatment are, indeed, the only means of increasing the recovery rate.

Diagnosis

Dargeon (1947) has drawn attention to the two types of children who should particularly bring to mind the possibility of malignant disease: those with an unusual symptom complex and those with a silent swelling.

Intracranial neoplasms. These tend to produce changes, either constant or, more characteristically, periodic, and these become evident when a child showing such changes is compared with others of his own age or with his own previous physical stature or behaviour. In children referred to child guidance clinics because of social maladjustment or alteration in psychic or mental state, change of disposition or habits, particularly if periodic, careful search should be made to exclude a brain tumour. Helmholz (1931) recorded that 50 per cent. of his cases of intracranial tumour had had symptoms for two to six months before the correct diagnosis was reached; 25 per cent. had continued for six to twelve months; and only 10 per cent. had been diagnosed within one month of the onset of symptoms. Yet 80 per cent. of them had papilloedema and 67 per cent. had clear radiological evidence of increased intracranial pressure.

The signs and symptoms of intracranial tumour in a child differ from those in an adult because the cranial sutures do not become firmly closed until the age of about ten years. In a child with such a tumour, therefore, the head tends to enlarge progressively, Macewen's 'crackpot' percussion sign is

TABLE 3
MALIGNANT DISEASE IN CHILDHOOD SHOWN AS A PERCENTAGE OF TOTAL ADMISSIONS TO DIFFERENT HOSPITALS

Hospital	Cases of malignant disease as a percentage of admissions	Cases of malignant disease in childhood as percentage of total admissions of malignant disease
Children's, Birmingham	0·53 (1937); 0·48 (1947)	—
Royal Manchester Children's	0·26 (1943–47)	—
Children's, Great Ormond Street ..	0·55 (1942); 0·6 (1947)	—
Children's Memorial, Chicago	0·13 (1921–45)	—
Adult hospitals:		
Christie, Manchester	—	1·1 (1941–45)
Middlesex, London	—	1·8 (1942)

present, and the skiagram shows convolution atrophy and separation of the cranial sutures.

Frontal headache is usually present but is of no localizing significance. Persistent headache, especially marked on waking, is a suggestive symptom. If there is also stiffness or tenderness of the neck, ophthalmoscopic examination should be immediately undertaken.

Ataxia is an important sign which is usually found in cerebellar tumours, and must be differentiated from the familial and other causes of cerebellar disturbance at this age.

Cyclic vomiting is another diagnosis which should not be accepted without taking the utmost care to exclude an underlying intracranial tumour. Some of Helmholz's cases had been diagnosed as cyclic vomiting, others had had appendicectomy performed because of the bouts of vomiting; many more had been treated for gastro-enteritis.

Of the many types of intracranial tumour which may occur, only two are at all common, medulloblastoma and astrocytoma. Both are subtentorial, the former usually being situated in the vermis and the latter in one of the cerebellar hemispheres. Medulloblastomas arise from embryonic rests situated just above the fourth ventricle. In the course of growth they distend the vermis and tend to spread into the meninges and spinal cord. They are greyish-red in colour, solid and vascular. They occur more commonly in boys and are rarely seen below the age of three years. In the last fourteen patients at the Christie Hospital, Manchester (Paterson, 1948), nine were boys and five were girls, the average age being nine years and the average duration of symptoms before treatment six months.

The first symptoms in these patients were: (1) vomiting in ten (cyclic in type in four of them), (2) headache in nine, (3) staggering in five, and (4) pain in the back or legs in four.

These patients were all treated by irradiation; five died within nine months; nine are alive and well after more than three years.

Williams (1946) reported eighteen medulloblastomas occurring in children, the average age being eight years. There were six recoveries in the series and treatment was by irradiation. Bailey et al. (1939), treated fourteen cases surgically with one recovery.

Astrocytomas are whitish-grey in colour, firm, and containing cysts with straw-coloured coagulating contents. They give rise to symptoms similar to those caused by medulloblastomas, but usually are of longer standing. If situated in one of the hemispheres there are, in addition, homolateral inco-ordination and nystagmus. Treated surgically the results are excellent. Bailey et al. reported eighteen recoveries out of twenty-one patients treated. Comparison between their results with astrocytomas and medulloblastomas suggests that surgery is the correct treatment for astrocytomas, but not for medulloblastomas. Paterson's results point to irradiation therapy as the best treatment for medulloblastomas. The prognosis varies according to the method of treatment adopted.

Neoplasms in other sites. Asymmetrical rate of growth of one part of the body, for example, an arm or a leg, or painless swelling of the abdomen or of a testis, is suggestive of a neoplasm. The common tumour of the testis is a seminoma (carcinoma), the chief symptom of which is slow and steady enlargement of the affected testis, with occasional periodicity. Pain is not a prominent feature. In children with undescended testes metastases may provide the first symptoms. The possibility of malignancy should be considered in any scrotal swelling occurring before puberty, and if there is any doubt the chest and abdomen should be carefully examined, together with a search for any enlarged lymph glands in the left supraclavicular fossa. The inguinal glands are not affected. It is important, similarly, that in every doubtful abdominal tumour in a boy the scrotum should be examined. Treatment is by irradiation followed by

orchidectomy, and the results are good. Williams recorded six patients of whom four were alive two and a half years or more later, and Dean found a five-year survival rate in more than three-quarters of his patients treated before metastases were evident. The Ascheim Zondek reaction is of help in diagnosing a seminoma, marked uterine enlargement occurring in the injected mouse.

Any non-traumatic swelling should be suspect, particularly a persistent adenopathy in the presence of negative Mantoux and Wassermann reactions. Any traumatic swelling which does not subside within a reasonable period of time should be similarly suspected. Progressive swelling of the abdomen in infancy, with the presence of a mass on palpation, occurs in over half the cases of Wilms's tumour, which is an embryonal adenosarcoma, resulting from a neoplastic exaggeration of the normal developmental process in the growth zone of the renal cortex in foetal life. Being encapsulated at first, this tumour causes few urinary signs in the early stages. It is a rapidly growing and vascular tumour, so that capillary rupture occurs easily and gives rise to haemorrhages within the tumour. Metastases are blood-borne, early and widespread, and the lungs and brain are particularly involved. It has been known to occur in a seven-month old foetus, but the average age of discovery is about three years. Boys and girls are affected almost equally, as are the two sides.

At the Christie Hospital there have been fifteen patients suffering from Wilms's tumour during the past seven years, eight boys and seven girls, and the average age was three years; eight tumours were left-sided and seven tumours right-sided. Of these fifteen patients five are alive and well after more than three years; ten patients died within two years. This tends to confirm the opinion of Ladd and White (1941) that a two-year cure is complete. They reported fourteen recoveries in sixty patients.

The first signs and symptoms noted were: (1) swelling of the abdomen in six patients, (2) haematuria in four patients, (3) abdominal pain in three patients; in two patients a mass was found in the abdomen on routine examination. The average duration of signs and symptoms before operation was four months. Five children had pre-operative irradiation in addition to the usual postoperative therapy. Of the ten patients who died, lung metastases were found in eight. It is important to remember that a palpable tumour may be the only diagnostic sign. Dean (1940) reported twenty-five patients suffering from Wilms's tumour and in no fewer than sixteen was the diagnosis made on routine examination.

Silver (1947) recorded eighteen cases, thirteen of which had nephrectomy; ten were alive from two and a quarter to fifteen years later. The youngest was an infant of three days in whom the tumour was so large that dystocia resulted. In one case pulmonary metastases appeared seven months after operation and disappeared after further irradiation, the child being alive and well two years later. In seven of the eight cases in which it was recorded, the blood pressure was raised. Nephrectomy restored it to normal, but it rose again with the appearance of metastases.

Wilms's tumour must be differentiated from the suprarenal neuroblastoma, which may present similarly as a mass in the abdomen. Metastases occur early, the liver, orbit, and skeleton being particularly involved. Like the renal embryoma (adenosarcoma), the neuroblastoma is highly malignant but is extremely radiosensitive, and Farber (1945) records recovery in ten out of forty patients. Recovery has even followed in patients in whom there had been liver metastases secondary to a primary suprarenal tumour proved histologically.

Retinal gliomas (retinoblastomas) are probably present at birth. The cells are similar to those of the partially differentiated cells of the foetal retina. These cells tend to be arranged in layers of from ten to twenty cells deep around the vessels. The cells in the peripheral layers may, therefore, die from lack of nutrition, and if the resultant necrosis becomes extensive it is possible for spontaneous cure to result.

Seventy-five per cent. of these cases are unilateral. They are not seen after the age of five years. The prognosis is good if the affected eye be enucleated before glaucoma has occurred. Williams reported twelve recoveries out of fourteen patients.

It has been suggested that if ophthalmoscopic examination were a routine part of every neonatal examination these tumours could be diagnosed at birth. As it is, 50 per cent. are diagnosable within the first two years of life, either by the presence of a dilated pupil in the affected eye, or by a white reflex, or by a squint. In bilateral cases the worse eye should be enucleated and the other one irradiated.

The early diagnosis of leukaemia, lymphosarcoma, and Hodgkin's disease (which are closely allied conditions) may be extremely difficult. Particularly is this so in leukaemia. Thrombocytopenic purpura, agranulocytosis, pertussis, acute infectious lymphocytosis, chronic non-specific infectious lymphocytosis, glandular fever, and congenital hypoplastic anaemia are some of the conditions which may have to be considered from the haematological point of view in the differential diagnosis. As not infrequently the peripheral blood picture in leukaemia may be inconclusive throughout the course of the disease, an examination of the bone marrow may be the only method of deciding with certainty. This investigation should be undertaken in any case in which doubt exists. Another common condition which may cause confusion is rheumatism, for the fever which may accompany leukaemia, together with the severe pain in the limbs and possibly also a haemic cardiac murmur, may easily lead to a mistaken diagnosis of rheumatism.

Skiagrams may be of help in diagnosing leukaemia, but not in the early stages. Caffey (1945) has drawn

attention to their value in cases showing splenomegaly and a persistent leucopenia with pyrexia. The radiological changes are most marked at the ends of the long bones, multiple areas of destruction being visible, due to masses of leukaemic tissue causing foci of rarefaction. The periosteum may also be elevated by leukaemic penetration which results in layers of bone beyond the cortical margin.

Biopsy is usually necessary to confirm the diagnosis of Hodgkin's disease and lymphosarcoma. Both these conditions may respond dramatically to radiation therapy, and this response may be considered to be of some diagnostic significance.

Malignant bone disease tends to occur in later childhood, and so far no form of treatment has been evolved which renders the prognosis anything but grave. Ewing's tumour and osteogenic sarcoma are often first diagnosed as osteomyelitis, and non-response to penicillin treatment, together with subsequent radiological changes, provide the clue to the correct diagnosis. Pain is usually a prominent symptom. A history of trauma is commonly obtained, but its significance must be open to doubt in view of the strictly embryonal character of most of the tumours.

The Origin of Malignant Disease in Childhood

Heredity seems to be a minor factor, except in retinoblastoma and neurofibromatosis (von Recklinghausen's disease), which, though usually considered benign, may undergo malignant changes.

Wells (1940), in studying the records of necropsies on 3,000 newborn infants, found four undoubted malignant neoplasms, all neuroblastomas (three suprarenal and one sympathetic), and he collected sixty-six authentic cases from the literature.

It is reasonable to suppose that, in view of the early age incidence, malignant disease in childhood is usually embryonic in origin. As in ordinary circumstances a large part of the life cycle, both of humans and experimental animals, is required to produce any type of malignant tumour, some changed condition must be present to allow such early and rapid growth. Faerber (1938) has remarked on the high glycolytic metabolism of embryos (and particularly their brains and renal medullae) and on the similar glycolysis in the metabolism of tumours. This may explain the early occurrence of retinoblastomas and neuroblastomas.

Topper (1947) has recorded an interesting observation on the basal metabolism of children with tumours. She found that all cerebral tumours, benign and malignant, were associated with a low basal metabolic rate and that all other malignant tumours caused a raised basal metabolic rate. Topper explains the lowered basal metabolic rate in intracranial tumours by assuming a reduction in the amount of pituitary hormone, possibly due in part to pressure. The raised metabolic rate in other malignant tumours is assumed to be due to the vigorous metabolism of the tumour cells themselves.

Characteristics of Childhood Tumours

Certain tumours occur almost exclusively in infancy and early childhood, for example, cerebellar medulloblastoma, nasopharyngeal fibroma, malignant suprarenal neuroblastoma, Wilms's tumour, and retinoblastoma. Others are much commoner than some of those occurring in later life, such as Ewing's tumour and many of the sarcomas.

Certain other tumours are extremely rare in childhood. Carcinoma, for example, forms but a very small percentage of the malignant tumours seen at this age period. At the New York Memorial Hospital, Pack and Lefevre (1930) found that of over 16,500 patients of all ages suffering from malignant tumours, 90 per cent. were carcinoma and 10 per cent. sarcoma, whereas in the paediatric department at the Mayo Clinic, Helmholz found only 3 per cent. of carcinoma as against 97 per cent. of sarcoma amongst over 700 children. Williams, in a series of 181 children, found 8 per cent. of carcinoma and 90 per cent. of sarcoma, and Dargeon in his series of 218 malignant tumours in children found 10 per cent. of carcinoma.

Except for those that are intracranial, most tumours occurring in children are either palpable or visible, thus differing markedly from the tumours occurring in adults.

Certain embryonic tumours may cease to be malignant, either spontaneously, or after irradiation. For example, as already mentioned, retinoblastoma may undergo spontaneous cure by extensive necrosis, and suprarenal neuroblastoma may no longer show any evidence of malignancy after irradiation. Reports of such cases, confirmed by biopsy, have been published by Cushing and Wolbach (1927) and others. Farber has also noted spontaneous maturation from malignant neuroblastoma to benign ganglioneuroma. The recurring nasopharyngeal fibroma undergoes regression spontaneously at about 20 years of age. On the other hand melanomas, which are benign in childhood, may become malignant at puberty.

Histological findings and clinical progress may be at variance. Steiner has emphasized that tumours occurring in childhood often exhibit a dissociation between malignant histology and benign clinical course, and also that tumours clinically appearing to be malignant, may show no histological evidence of malignancy. For example, the recurring nasopharyngeal fibroma is histologically benign, yet it is undoubtedly a malignant growth.

There is a tendency to rapid progress and wide metastasis in childhood tumours, and although most of the growths are radiosensitive there is a liability to recurrence after treatment and careful watch must therefore be kept by periodic examinations, and further treatment instituted promptly if such recurrence becomes evident.

One important difference between tumours of children and of adults is that as children are still in process of growth this may be affected either

locally or generally and either excessive or diminished in rate, according to the site of the tumour, for example, pineal, pituitary, or gonadal.

Treatment

Treatment will naturally vary according to the nature of the growth and to its position and extent. It may be considered under two headings: (a) curative and (b) palliative. In the main, curative treatment will consist in irradiation or surgery or a combination of the two. If combined, irradiation may precede or follow surgery or it may be used both before and after operation. Palliative treatment will be similar, but will also include nitrogen mustard, urethane, and radioactive isotopes.

Special care must be taken in irradiation therapy; the dangers of damage to the haemopoietic system, to the epiphyses of a growing child, and to the gonads must constantly be borne in mind.

Prognosis

The prognosis varies, as might be expected, with the nature and accessibility of the tumour, the age of the child, and the length of time before treatment is started. Excluding the leukaemias, cures of practically every type of malignant neoplasm have been reported. The figures of recovery also show considerable variation. Dargeon, for example, reported eighteen cures (average duration over eight years) in his series of 218 patients with malignant disease of all types, and Williams reported sixty cures out of a series of 167 patients.

Summary

With advances in prophylactic paediatrics and the advent of the sulphonamides and antibiotics, there has been a marked difference in the last ten years in the position occupied by malignant disease as a cause of death in childhood compared with, for example, cerebrospinal meningitis, whooping-cough, measles, and diphtheria. Although there is no evidence of any increase in the total number of deaths from neoplasms, which remain rare in paediatric practice, the decline in mortality from the infectious fevers has thrown into relief the importance of malignant disease. A malignant disease may be defined as one which, untreated, leads to death of the patient either from metastasis or by direct spread.

It is still a common belief that all malignant diseases are incurable; such is no longer the case. Isolated cures have been reported in tumours of almost every form and site but, what is more important, certain types, if treated early enough, may now be said to carry an increasingly good prognosis. This is particularly true in the youngest age-groups (from birth to five years).

Although malignant disease can occur in children in any part of the body in which it appears in adults, there are certain selective sites for this disease in children, and there are some tumours which occur in childhood only. Heredity would appear to be a factor, particularly in retinal glioma (retinoblastoma) and neurofibromatosis.

Childhood tumours grow rapidly and often metastasize widely. Because of the tendency to recurrence both locally and by metastasis, close watch must be kept after treatment in order that immediate irradiation may be given at the first evidence of such recurrence.

They differ from adult neoplasms, in that they occur during the period of active growth of the host and may, by their site, materially affect growth or metabolism.

Intracranial tumours form a considerable proportion of childhood neoplasms; their symptomatology differs considerably from that of adults.

Treatment of malignant disease may be curative, or palliative. Curative therapy consists essentially in surgery, or deep x-ray therapy, or a combination of the two. An increasing range of palliative measures is becoming available for those cases unsuitable for surgery or irradiation.

I am greatly indebted to Dr. Edith Paterson of the Christie Hospital, Manchester, for her help and advice in preparing this paper and for allowing me access to the hospital records. My thanks are also due to Professor J. M. Smellie and his registrar, and to Dr. M. Bodian for providing the Birmingham and Great Ormond Street figures quoted.

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BROMSULPHALEIN EXCRETION IN THE NEWBORN

BY

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Ever since Yllpø published his valuable contribution to the subject of icterus neonatorum in 1913, it has seemed almost certain that the liver of the newborn infant is far less efficient than that of the adult in excreting bile pigment. Nevertheless very few direct studies of the excretory capacity of the liver of the newborn infant have been made, and the work reported here was carried out in the early part of 1947 under the impression that there were no previous studies of bromsulphalein excretion in the newborn. However, before the work was completed it was discovered that Herlitz had carried out bromsulphalein tests as long ago as 1926 and that more recently Salmon and Richman (1943) had worked on the problem. Our results were seen to be very similar to those of Herlitz, who found a definite impairment of excretion in the newborn, but in view of the fact that the findings of Salmon and Richman were altogether different it was felt worth while to complete the work and to present it.

Methods

Clinical material. Fourteen normal newborn infants were tested. Between one and five hours after birth the umbilical cord was cut across and, with careful aseptic precautions, a fine plastic catheter was passed up the umbilical vein for a distance of two to three inches. Bromsulphalein was then injected in a dose of 5 mg. per kg. body weight made up in 0·5 per cent. solution; (in two out of the fourteen infants the dose was reduced to 3 mg. per kg.). The catheter was left in situ for periods up to two hours, and blood samples were obtained at various intervals after withdrawing 1 to 1½ ml. of blood through the catheter to rinse it. In some cases the catheter was withdrawn after the initial injection and a new catheter passed later to obtain the blood samples. The cord was then tied in the ordinary way. Samples taken more than two hours after the injection were obtained from the external jugular vein or by pricking the warmed heel. The procedure did not appear to upset the infants in any way, and in no case was there any interference with the rapid, healthy scarring of the umbilicus.

The icteric indices of the cord blood and of blood samples taken at intervals during the following six days of life were also determined.

Ten normal adults were also tested; the object of this was twofold: firstly to obtain control material to compare with the findings in infants, in case our technique should yield slightly different results from those of other workers; secondly, to discover whether the withdrawal of samples through a plastic catheter through which bromsulphalein had been injected, would give falsely high results. To test this latter possibility, a catheter was introduced into an arm vein through a wide-bore needle and then passed up the vein for about 6 inches; bromsulphalein (5 mg. per kg.) was injected and blood samples were withdrawn through this catheter. Simultaneously, blood samples were taken from the opposite arm by ordinary venepuncture.

Estimation of bromsulphalein. The bromsulphalein content of samples was measured in a photo-electric colorimeter using a green filter (0 gr. I, Chance). After adjusting the galvanometer reading to zero with diluted serum in the optical cell, one drop of 20 per cent. NaOH was added and the galvanometer deflection noted. A calibration curve was prepared by testing known dilutions of the injection solution. The relationship between bromsulphalein concentration and the extinction was almost linear with concentrations below 0·8 mg. per cent. Plasma samples were suitably diluted with sodium sulphate before measurement, to bring their concentration below this level.

Many control tests were made to discover to what extent the optical density of normal plasma was altered by the addition of alkali. It was found that when testing undiluted plasma, differences as great as plus or minus 0·05 on the log scale might occasionally be produced, though with diluted plasma the deflections were smaller. Under the conditions of the test, this meant that amounts of the dye equivalent to less than 0·13 mg., that is to say 1·3 per cent. of the standard (see below), could not be detected with certainty. In the tabulation of results, amounts estimated as being less than 2 per cent. of the standard have therefore been described as 'nil'.

To conform with convention the results are expressed as percentages of a 10 mg. per cent. standard when using a 5 mg. per kg. dose. In the two cases where a 3 mg. per kg. dose was used the

TABLE 1

PERCENTAGE RETENTION OF BROMSULPHALEIN AT INTERVALS AFTER INJECTION

		5–8 minutes	15–17 minutes	30–40 minutes	55–70 minutes	2 hours	4–6½ hours	24 hours
A. 12 infants receiving a dose of 5 mg./kg.; standard=10 mg. %	1	—	—	26	—	—	—	—
	2	58	—	20	19	—	—	—
	3	35	—	20	23	—	—	—
	4	64	—	—	18	—	11	2
	5	66	36	24	21	19	15	7
	6	57	34	18	—	15	—	2
	7	65	40	—	—	19	—	—
	8	53	22	12	—	10	—	2
	9	49	19	15	16	14	—	Nil
	10	112	30	16	—	9	—	2
	11	85	41	25	—	19	—	—
	12	91	45	—	—	—	14	—
	Av.	66·8	33·4	19·6	19·4	15·0	13·3	2·5
B. 2 infants receiving a dose of 3 mg./kg.; standard=6 mg. %	13	43	—	13	—	8		
	14	44	—	16	—	12		
		5 minutes	15 minutes	30 minutes	60 minutes	Type of subject		
C. 10 adults receiving a dose of 5 mg./kg.; standard=10 mg. %	15	64	8	3	Nil	Healthy adult		
	16	51	10	Nil	Nil	Healthy adult		
	17	60	16	Nil	Nil	Healthy adult		
	18	75	31	4	Nil	Healthy adult		
	19	—	14	2	Nil	Healthy adult		
	20	—	19	7	2	Healthy adult		
	21	51	—	Nil	Nil	Recently delivered woman; convalescent from pneumonia		
	22	50	—	12	12	Recent caesarean section: mild diarrhoea recently		
	23	49	11	2	Nil	Convalescent from herniotomy		
	24	56	16	4	2	Convalescent from herniotomy		
	Av.	57·0	15·6	3·8	—			

results were referred to a 6 mg. per cent. standard. Although it is usual to use a 10 mg. per cent. standard for a 5 mg. per kg. dose, it is clear that with a plasma volume of approximately 45 ml. per kg. (DeMarsh et al., 1942) the theoretical maximum value is in fact rather higher; doubtless this explains the finding in one of our infants of an initial concentration of 11·2 mg. per cent.

Determination of icteric index. The principle of Ernst and Forster (1924) was used. 50 c.mm. of serum was added to 0·2 ml. of acetone, mixed well, and centrifuged. The colour of the supernatant fluid was compared with that of standard solutions of potassium bichromate in small tubes of uniform bore. This crude method was used because it needed only very small amounts of blood and because we were only interested in detecting gross differences.

Results

The results in infants and adults are set out in table 1 and summarized in fig. 1. It will be noted that in the infants the amount of dye fell to about 20 per cent. of the standard in thirty to forty minutes but thereafter the rate of disappearance was very slow, so that the average retention in seven infants two hours after injection was 15 per cent. In a few cases samples were taken from infants twenty-four hours after the injection, and in several of these there was a strong suggestion that traces of dye were still present, though the method of estimation made it impossible to be certain of the interpretation of small galvanometer deflections. In two cases where samples were taken from the same infant at approximately thirty minutes, sixty minutes, and twenty-four hours the log of the percentage retention was plotted against time and it was noted

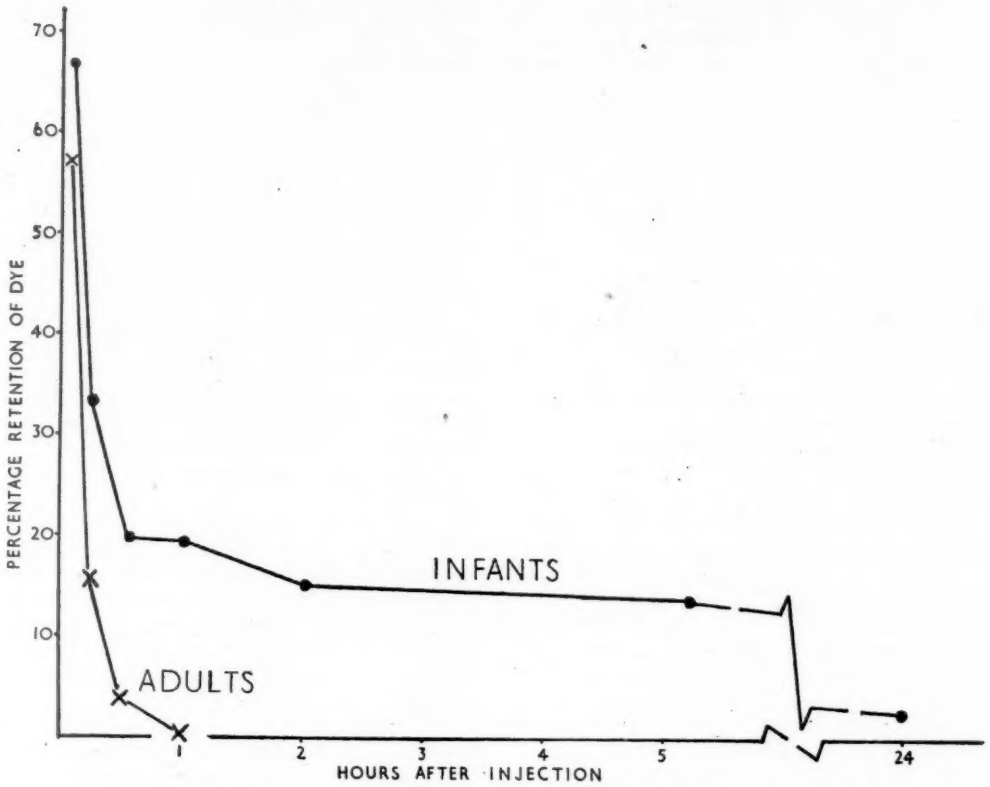

FIG. 1.—Bromsulphalein excretion in healthy infants and adults after a dose of 5 mg. per kg. of body weight 100 per cent. = 10 mg. per cent.

TABLE 2

BROMSULPHALEIN RETENTION IN TWO GROUPS OF NEWBORN INFANTS

	Case No.	Percentage of bromsulphalein retained at :		
		½ hour	1 hour	2 hours
A: group in which the icteric index was 16 or less three days after birth	2	20	19	—
	6	18	—	15
	9	15	16	14
	10	16	—	9
	12	—	—	14†
	14*	16	—	12
B: group in which the icteric index was 32 or more three days after birth	1	26	—	—
	3	20	23	—
	4	—	18	—
	5	24	21	19
	7	—	—	19
	8	12	—	10
	11	25	—	19
	13*	13	—	8

* These two infants received a dose of 3 mg. per kg., the rest received 5 mg. per kg.

† This sample was taken four hours after injection.

that the estimates fell upon straight lines. This suggests that the rate of disappearance of bromsulphalein, after the initial phase of rapid removal, is proportional to the concentration.

By contrast, in adults, only about 4 per cent. of the dye was left in the plasma thirty minutes after injection and only 1 per cent. or less was present at sixty minutes. However, one exceptional case (Case 16) still had 12 per cent. of the dye in the plasma after sixty minutes; this result is discussed below.

That the amount of dye found in the infants' plasma was not due to the method of obtaining the blood samples was shown by the results in those adults in whom the samples were obtained through a catheter; in these, negligible differences were found between samples taken through the catheter and samples taken from the opposite arm. Moreover, a few samples taken from infants from the external jugular vein or from skin prick two to four hours after injection all contained amounts of the dye corresponding to between 10 and 20 per cent. of the standard.

In fig. 2 the course of the icteric index changes in all the infants is plotted; it will be seen that the cases conveniently fall into two groups, namely those whose icteric index was 16 or lower on the third day of life and those whose index at the same time was 32 or higher. In table 2 the cases are divided into these two groups and the bromsulphalein retention at thirty to forty minutes and one to two hours is compared. The numbers are too small for statistical analysis but it is evident that there are no gross differences.

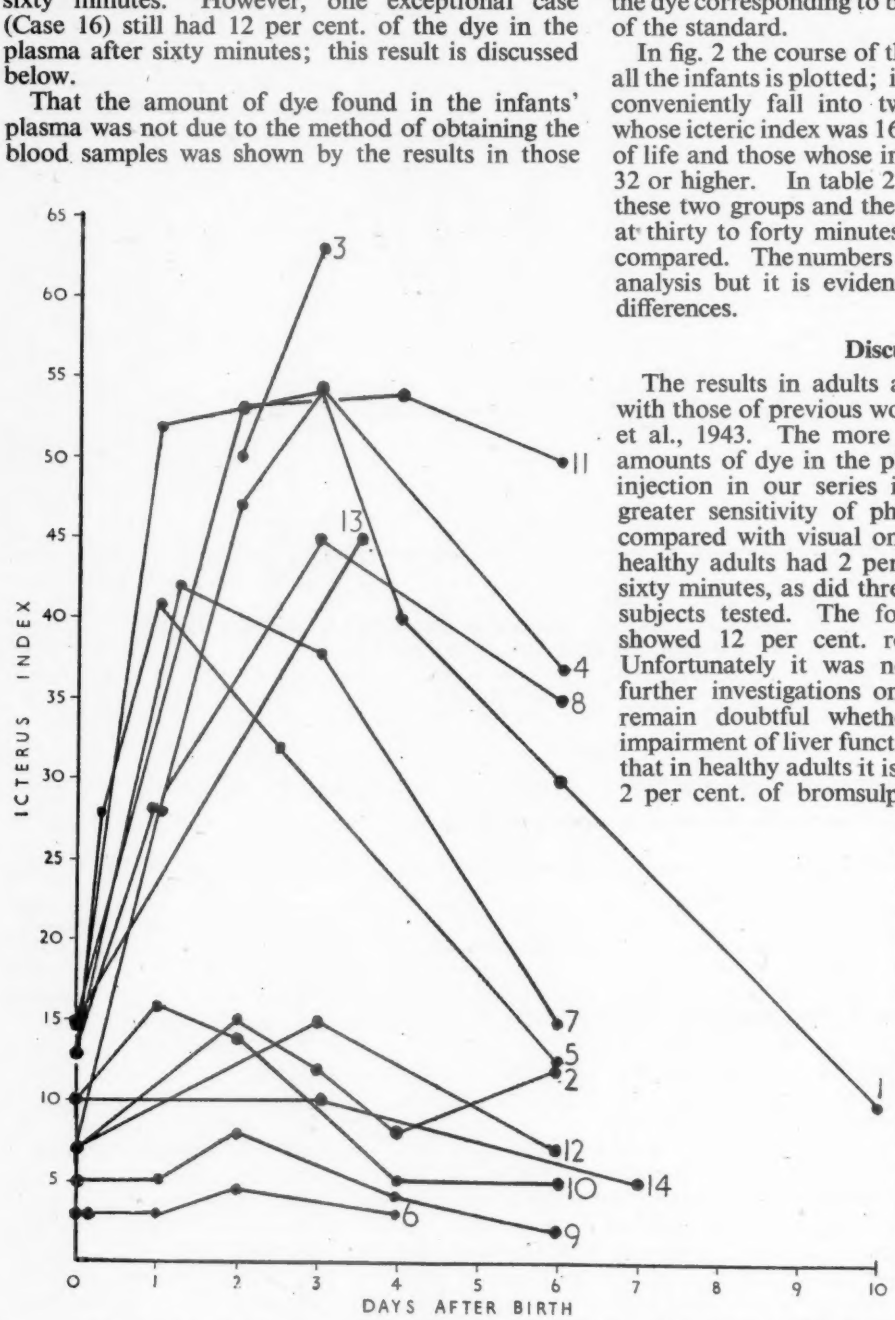

FIG. 2.—Observations of icteric index during the first few days of life in fourteen healthy infants whose bromsulphalein excretion during the first few hours of life was measured.

Discussion

The results in adults are in essential agreement with those of previous workers, for example Mateer et al., 1943. The more frequent finding of small amounts of dye in the plasma thirty minutes after injection in our series is presumably due to the greater sensitivity of photo-electric measurements compared with visual ones. In our series, all the healthy adults had 2 per cent. or less retention at sixty minutes, as did three of the four convalescent subjects tested. The fourth convalescent subject showed 12 per cent. retention at sixty minutes. Unfortunately it was not possible to make any further investigations on this patient and it must remain doubtful whether she had in fact any impairment of liver function. In any case it is clear that in healthy adults it is unusual to find more than 2 per cent. of bromsulphalein retained one hour after injecting a dose of 5 mg. per kg.

By contrast, in newborn infants receiving the same dose there was an average retention of 15 per cent. of the dye two hours after injection. This result unequivocally supports the contention of Herlitz that bromsulphalein excretion is greatly delayed in the newborn. Herlitz used a dose of 2 mg. per kg. and found 20 to 30 per cent. retention of the dye at thirty minutes in the five infants which he tested within twenty-four hours of birth. This agrees fairly well with our figures of 12 to 26 per cent.

retention at thirty to forty minutes in nine infants receiving a 5 mg. per kg. dose and with our finding of 13 and 16 per cent. retention at thirty minutes in two infants receiving a 3 mg. per kg. dose; in both the latter infants there was an appreciable amount of dye (8 and 12 per cent.) at two hours after injection. Neither our results nor those of Herlitz can be reconciled with those of Salmon and Richman (1943) who reported the rapid complete elimination of bromsulphalein within about twenty minutes of injecting a dose of 2 mg. per kg. into infants from one to eight days old. Possibly the use of a visual method may have prevented the detection of relatively small amounts of dye.

It is of interest that Aballi and Castellanos (1925) carried out tests in infants one to two days old with phenoltetrachlorphthalein and found some retention of the dye sixty minutes after injection, whereas in infants aged two years or more there was no retention.

Our results add to the findings of Herlitz by demonstrating that the clearance of bromsulphalein from the plasma in the newborn is still incomplete five hours after injection and, in some cases, is still incomplete twenty-four hours after injection. They also agree with those of Herlitz in demonstrating no appreciable difference in bromsulphalein retention between those infants who develop jaundice and those who do not.

In the presence of hyperbilirubinaemia, a delayed excretion of bromsulphalein must be interpreted cautiously. Dragstedt and Mills (1936) have shown that after the injection of bilirubin into animals with normal liver function the excretion of bromsulphalein is delayed. Since the infant's plasma at birth contains on the average about 1·7 mg. per cent. of bilirubin (Davidson et al., 1941), some three times the average adult level, it might be contended that the infant's liver at birth is already occupied in excreting bilirubin to such an extent that an impaired excretion of bromsulphalein would be expected. However, this explanation will scarcely do for those two of our infants who had icteric indices in the cord blood of 5 or less and who subsequently showed no appreciable rise. These infants must have had bilirubin values well within the normal adult range (their plasma was almost colourless), and in them the diminished bromsulphalein excretion must be otherwise explained. Herlitz considered that an immaturity of the reticulo-endothelial system in the newborn was the explanation, but it seems to us more likely that the cause lies in an immaturity of the excretory function of the newborn liver. It has long been known that the ability of the newborn infant to excrete bile pigment is low (Yllpø, 1913; Snelling, 1933), and it seems extremely likely that the poor excretion of bromsulphalein is a reflection of this.

In adults, bromsulphalein is removed from the bloodstream in two phases, an early very rapid phase and a second slower phase. There is some evidence that the first of these two phases is due to the removal of dye by the R-E system whereas the second depends upon the excretory capacity of the liver (Wirts and Cantarow, 1942). It will be noted that in the infants studied the initial phase of removal was only slightly less rapid than in adults but that the second phase was strikingly slower. It seems probable, therefore, that the difference between the rate of removal of bromsulphalein in adults and newborn infants is due to a lower excretory capacity of the liver in the infant.

Summary

1. Bromsulphalein injected into infants a few hours after birth is removed from the plasma far less rapidly than in adults.

2. This finding is most probably to be explained by an immaturity of the excretory function of the liver in the newborn.

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LIVER FUNCTION IN NEWBORN INFANTS

WITH SPECIAL REFERENCE TO EXCRETION OF BROMSULPHALEIN

BY

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The theory that neonatal jaundice is produced mainly by haemolysis of excess red cells present at birth has been strongly criticized in recent years (Weech, 1947; Findlay, 1946) and increasing emphasis has been placed on the role of the liver in the genesis of this form of jaundice (Weech ; Findlay; Mollison, 1948). Direct evidence that the liver in newborn infants is unable to function adequately is, however, scarce and somewhat contradictory (see Weech for references). It was felt that investigation of the functions of the liver in newborn infants with special reference to its excretory capacity might help to clarify the position.

Material and Methods

BROMSULPHALEIN EXCRETION TESTS (Rosenthal and White, 1925; Mateer et al., 1943). These were carried out on normal full-term infants at the Boston Lying-in Hospital. The infants were between 8 and 216 hours old. Single determinations were made on the majority of the infants but a few had two tests and two infants had three tests. The test dose of 5 mg. of dye per kg. body weight was injected into a scalp vein and a sample of 0·2 to 0·3 ml. of blood was taken forty-five minutes later from a stab wound in the heel into a glass tube of 2 mm. internal diameter and 10 cm. long; small rubber caps were used to close the ends of the tube. The serum was removed after centrifuging and the bromsulphalein level was determined by the method described by Gaebler (1945) but the microcolorimeter attachment of the Evelyn photoelectric colorimeter was used instead of the macrocolorimeter, the volumes being adjusted accordingly (0·1 ml. serum, 0·5 ml. water, and 0·6 ml. of 0·1N NaOH). It was thus possible to make measurements on capillary blood, a useful consideration in the newborn infant. Preliminary measurements on capillary blood and venous blood taken simultaneously at varying intervals after injection of dye showed that the results were in agreement so long as the blood from the heel was flowing freely when collected.

Percentage retention of the dye was calculated according to the method of Gaebler (10 mg. per 100 ml. serum = 100 per cent. retention).

OTHER TESTS. In addition, samples of about 5 ml. of blood were taken from the internal jugular vein of thirty-two other infants from one to seven days old and the following tests carried out on the serum: (a) thymol turbidity and thymol flocculation (Maclagan, 1944); (b) cephalin cholesterol flocculation (Hanger, 1939; Neefe and Reinhold, 1944); (c) colloidal gold (Maclagan, 1946).

'One minute' and total serum bilirubin levels were measured in most of the infants in both groups using the photoelectric colorimeter (Malloy and Evelyn, 1937; Watson and Hoffbauer, 1947).

Results

Bromsulphalein excretion tests. The figure shows the results for all the eighty-three tests that were done. It is apparent that during the first four days of life most of the babies showed much more retention (i.e. less excretion) than did the babies of four to nine days of age. The results are arranged in the table to show the number of babies in each of three different age groups having retention of dye above and below the mean retention for the whole group. Calculation of the χ^2 value shows that this distribution of results is most unlikely to have arisen by chance ($p < 0·01$).

It should be noted that even the babies of four to nine days showed more retention than that

* This work, carried out in the Liver Function Laboratory of the Children's Medical Centre, has been supported by a grant from the Diabetes Fund.

regarded as normal for healthy adults using the same dosage of dye (Mateer et al., 1947).

The babies who had more than one test showed results in essential agreement with those already given. Of those that had two tests (on the first and third day of life), none showed more retention on the second test and some showed less. The two babies who had tests on the first, third, and seventh day showed about 14 per cent. retention on the first and third day and about 6 per cent. retention on the seventh day.

There was no correlation between the results of the bromsulphalein tests and the levels of serum bilirubin. It would have been of interest to measure bromsulphalein retention on the first day of life of a large number of infants and to determine whether this was related to the height of the subsequent rise in bilirubin levels, but this was not possible at the time the experiment was conducted.

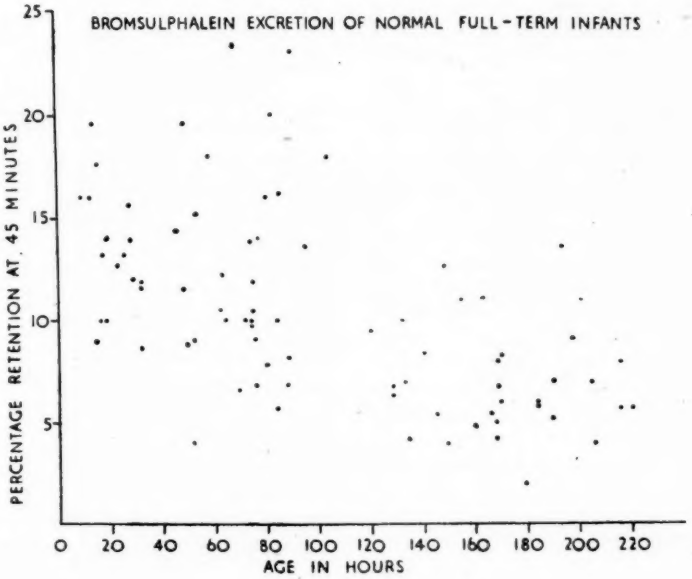
There was no correlation between the retention of dye and the weight of the babies.

Other liver function tests. None of the other tests showed any abnormal results whatsoever.

Discussion

Mollison (1948) showed that the infant's red cells are destroyed after birth about twice as quickly as are red cells obtained from adults but that this of itself would not account for all the rise in serum bilirubin level in the newborn period unless the liver were unable to excrete all the extra load of bilirubin thus produced. He found also that appreciable amounts of bromsulphalein persisted in the serum two hours after injection into infants soon after birth. Fashena (quoted by Weech, 1947), using a method of calculation devised by Weech et al. (1941), showed poor excretion of injected bilirubin in the first few days of life with subsequent improved excretion.

The results of the bromsulphalein tests here recorded are in general agreement with those of Herlitz (1927) who found poor excretion in the youngest infants and no correlation with the presence or absence of jaundice; the excretion was better in older infants. They apparently differ widely from the results reported by Salmon and Richman (1943), but the curve of bromsulphalein excretion given in their report is a composite one from the results in infants of various ages in the newborn period and it is impossible to determine from their data how many of the readings taken twenty minutes or more after the dye was injected were made on infants during the first two or three days of life.



TABLE

RESULTS OF BROMSULPHALEIN EXCRETION TESTS IN NEWBORN INFANTS

Age of infants (hours)	Bromsulphalein retention at 45 mins.		No. of infants tested
	Above mean	Below mean	
	Number of infants		
8–48	16	5	21
49–96	12	16	28
97–216	6	28	34
Total	34	49	83

Mean bromsulphalein retention (all tests) 10·2 per cent.
$\chi^2 = 20{\cdot}6$ (value for $p = 0{\cdot}01$ 9·2)

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Dragstedt and Mills (1936) have criticized the use of the bromsulphalein excretion tests in jaundiced subjects on the grounds that the raised serum bilirubin of itself interferes with the excretion of dye. While this factor may have accounted for some of the high retention levels found on the third and fourth days it could not account for the even higher levels on the first and second days when the bilirubin levels were lower.

The fact that even the babies of four to nine days showed retention greater than that reported for adults suggests that there is a continuing difficulty in excretion. Herlitz (1926) found delayed excretion up to the age of five months.

It is important to note that the function here concerned is that of excretion and that our results give no evidence of poor function in other respects. We were unable to confirm the positive findings with the cephalin cholesterol flocculation tests reported by Salmon and Richman. Thymol turbidity and flocculation tests and colloidal gold tests have not been carried out previously on newborn infants so far as we are aware.

We can at present only speculate as to the possible cause or causes of the retention of dye. It may be related to circulatory adjustments taking place in the first few days after birth, since it is known that circulatory factors are of importance in the excretion of the dye (Blumberg and Schloss, 1947). In view of the negative results with the other tests it seems unlikely that the liver cells are damaged. The continued poor excretion of the dye after the first four days suggests that the liver may be ' immature ' as regards its excretory function but the rapid improvement in the first few days makes it appear likely that some other factor is also involved.

Summary

Eighty-three bromsulphalein excretion tests have been carried out on full-term infants from 8 to 216 hours old. The younger infants showed greater retention of dye than did infants over four days of age: the results are statistically highly significant. The infants over four days old showed greater retention than that reported for adults given equivalent amounts of dye.

There was no correlation between the amount of dye retention and the level of serum bilirubin or between the amount of dye retention and the weight of the infant.

Thymol turbidity and thymol flocculation tests, cephalin cholesterol flocculation tests, and colloidal gold tests carried out on the serum of thirty-two other infants of the same age range showed no abnormality whatever.

We wish to record our thanks to Dr. Duncan Reid, Dr. Stewart Clifford, Dr. Clement Smith, and Miss Twomey, Nursery Supervisor, for help with the carrying out of tests.

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LIVER DAMAGE IN GASTRO-ENTERITIS

BY

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Jaundice in gastro-enteritis is described as a rare terminal event (Sakula, 1943) and has been commonly regarded as a manifestation of septicaemia, as for instance in Buhl's disease (Capon, 1934). Recent advances in our knowledge of liver disease, particularly in relation to malnutrition, cast considerable doubt on this explanation, and Bonham-Carter (1947) has pointed out the significance of the various pathological changes which are found in the liver in fatal cases of gastro-enteritis. There is some reason to believe that the post-mortem appearances of cell damage, fatty infiltration, and early fibrosis which have been described, alone or in combination, depend to some degree on the severity and duration of the disease. This cannot be confirmed until the exact sequence of events is defined by a systematic study of liver biopsy material.

The purpose of this paper is to put forward further views regarding the cause of these liver complications, based chiefly on clinical observation, and to describe a method of treatment which has proved successful in a condition which up to the present has almost inevitably proved fatal.

In five of the six cases about to be presented, clinical evidence of severe liver damage was found. In the sixth some of the features which can be recognized as a syndrome were lacking, but as it compared so closely in other respects to the group as a whole it has been included in the series.

Potassium deficiency was the other striking change and was present in all six patients. The serious effect of loss of this salt from the system in gastro-enteritis and the reduction of mortality when it is made good have been described by Darrow (1946). We have confirmed this in many instances without obvious liver failure, but its association in the present series is noteworthy and calls for consideration of a possible relationship.

Clinical Picture and Incidence

Enlargement of the liver, which often appeared rapidly, jaundice, and haemorrhagic phenomena associated with a low prothrombin time were taken as evidence of liver damage. Oedema followed a constant initial stage of dehydration and was considered to be closely related to the general metabolic disturbance. Speculation as to the cause and effect would be premature, since arguments can be deduced only from the beneficial results of combined therapy. The duration of gastro-enteritis before the onset of these complications was variable. In four infants profuse diarrhoea with some vomiting had been present from two to three weeks; in two others a much longer gastro-intestinal upset was reported. In all six the chance of any serious underlying defect is rendered unlikely by their after-history.

Severe pyogenic infections developed in four cases, but only in one was a focus present before the onset of liver damage. Polymorphonuclear leucocytosis was found at the height of the disturbance. It is a feature of acute liver failure in adults and need not, therefore, mean infection in our cases. There was no evidence of urinary infection except in Case 5, where it occurred late in the disease and was one of a number of secondary septic complications. An erythematous rash was present in two cases, both of whom were receiving various drugs at the time, including potassium, but it did not conform to the description of a diffuse erythema from potassium over dosage (Govan and Darrow, 1946), and the serum potassium was never abnormally raised. In all cases there was severe dehydration. Oedema was often gross at the worst stage of the illness.

Variations from the typical clinical picture just described were also encountered. Jaundice was absent in one instance (Case 3), a haemorrhagic tendency was lacking in another (Case 2), and in a third (Case 4) the only definite evidence of liver impairment was a raised serum bilirubin. Minor degrees of the condition undoubtedly occur, and in seventy consecutive cases of gastro-enteritis observed over the same period without obvious liver failure, three had a raised serum bilirubin (1 or 2 mg. per cent.) and three produced altered blood in the stool or vomit as special isolated features. In one other there was prolonged bleeding from an intravenous wound and a lowered prothrombin index. Considerable enlargement of the liver was also discovered in some severe cases with subsequent reversion to normal size without special treatment. It appears, therefore, that any idea of the incidence depends on the criteria used and the care with

which they are sought in the diagnosis of the disorder.

The cases presented in this paper had an easily recognizable clinical picture probably because they were extreme examples of the condition. Jaundice from our experience is a most ominous sign, and unless energetic treatment is undertaken is always liable to end fatally. Before its true significance was realized, this complication was noted in eight out of 300 cases of gastro-enteritis treated in the hospital during the last two years. Only two of the eight survived. In another series of 159, seven developed jaundice and died (Giles and Sangster, 1948). Of 216 cases described by Gairdner (1945), twenty-three became jaundiced, again with a uniformly fatal result.

Clinical Investigations

A regular procedure was adopted in examining our cases and will be found incorporated in the charts which follow. Reference here will be made only to those clinical findings and investigations which presented some difficulty in accurate interpretation.

LIVER SIZE. This was measured in finger-breadths below the costal margin, changes being recorded only when they could be recognized as certain. A liver palpable at one finger's-breadth is generally regarded as normal for an infant. Though alterations within this limit may be significant, other factors such as the level of the diaphragm must be taken into account.

DEHYDRATION. The degree of dehydration is always difficult to estimate clinically. In our cases the notation + + + is reserved for the most severe examples of the condition, while a single + indicates a significant loss of skin elasticity.

OEDEMA. This is recorded only when its distribution was general.

DIARRHOEA. In diarrhoea the number of stools alone can be misleading; therefore definite alteration in their character is also mentioned in the protocols.

PLASMA PROTEIN. This was measured by the specific gravity method.

PROTHROMBIN TIME. This was calculated as a prothrombin index (Innes and Davidson, 1941) which has fallacies but was found a sufficiently reliable test when repeated for comparison in the course of the disease, and has obvious advantages in the simple technique and the small amount of blood required.

LIVER FUNCTION TESTS. No special liver function tests were carried out as a routine. In the earlier fatal cases, to which reference has been made, the alkaline phosphatase was only twice higher than twenty and the thymol turbidity normal more often than not.

Pathogenesis

LIVER DAMAGE. A parenteral pyogenic focus of infection can be excluded as it was present only in one case in our series at the relevant stage. Bonham Carter's observations on post-mortem material give further support to the view that septic infection plays no major part in the cause of this complication, as in half his cases there was no evidence of such infection. Virus liver disease produces its own characteristic picture, quite unlike the syndrome we have described. The possible effect of toxic amines produced by abnormal enzyme activity of bowel flora (Gale, 1940) remains an open question.

Some nutritional deficiency seems to be the most likely factor and would fit in best with the course of the disorder and the limited histological investigations of the liver which have been made. If this were the pathological basis a good response might be expected to therapy which aims at restoring essential elements in the diet, since these, in common with all the food offered, have been largely lost through diarrhoea or vomiting.

As already stated, it is not possible as yet to present a clear picture of the morbid anatomy of the liver. In a few fatal cases in the past which we have studied the histological changes have not been constant and did not fall into one of the distinct groups so well defined by Himsworth (1947). In fact a number of changes have been found, not necessarily in association, namely fatty infiltration, dilation of sinusoids, parenchymal degeneration, and cellular necrosis with round cell infiltration. Early fibrosis was also occasionally present.

By analogy with experimental work and with the recent descriptions of fatty liver disease of infants in the tropics, lack of a lipotropic agent would appear to be the most likely cause of hepatic complications in gastro-enteritis. Fatty infiltration would well explain the slow return of the liver to its normal size under appropriate treatment. On the other hand it would not explain the acute onset of symptoms, rapid enlargement of the liver, and grave course of the disease, which are more in favour of a process resembling acute necrosis. Therefore, both on clinical grounds and from the post-mortem evidence, there is some reason to believe that the liver lesion in gastro-enteritis may combine features of the two main types of damage known to occur in experimental and human examples of hepatic disease.

DISTURBANCES OF FLUID BALANCE. In liver disease a high water content is characteristic of the lesion known as massive necrosis (Himsworth, 1947), and is thought to be a result of pathological change within the cell. In gastro-enteritis puzzling shifts of tissue fluid are related to electrolytic imbalance, where loss of intracellular potassium is the prime cause and transfer of sodium from the extra- to the intracellular compartment with reduction in the extracellular fluid an effect (Darrow et al., 1948). Although in most experimental procedures the change takes place chiefly in the muscles, its occurrence in the human liver in states of dehydration and shock is a possibility (Darrow, 1945).

The oedema of malnutrition can no longer be

regarded as a simple osmotic effect of hypoproteinaemia (Denz, 1947; Henschel et al., 1947), and this is in general borne out by the inconstant relationship of plasma protein level to the occurrence of oedema in our cases. All of them were given oral or intravenous fluid but seldom more than was adequate for their needs and to make good their continued losses. Therapeutic over-hydration cannot, therefore, be accepted as a cause of the oedema. There was never any clinical suggestion of cardiac failure.

A low serum potassium was present in all cases and it should be stressed that a normal serum level does not necessarily exclude cellular deficiency (Miller and Darrow, 1940). Exactly how potassium loss occurs in gastro-enteritis is not fully understood; certainly it is out of proportion to the degree of tissue destruction and quantity passed in the stools (Darrow, 1946). We have observed two effects in all forms of gastro-enteritis when such a deficit is not made good: difficulty in rehydration despite massive quantities of fluid by any route, and a tendency to oedema. Administration of potassium orally or in urgent cases intravenously, brings about a rapid return to normal and points to potassium as an important determining factor in the proper distribution of water.

HAEMORRHAGE. Except in Case 3, in which the bleeding time was prolonged, investigation was confined to the prothrombin time. Haemorrhage from the bowel or stomach mucosa was clearly related to hypoprothrombinaemia and was quickly controlled soon after treatment began. Hypocalcaemia was not found.

To summarize our ideas of the pathogenesis, we believe that infants who survive the acute period of severe dehydration have necessarily passed through a severe state of malnutrition and may thus readily suffer from liver failure later in the course of their disorder. Should they succumb, histological evidence of liver damage might be expected and has in fact been found. Clinically, minor degrees of this complication have been mentioned, where presumably the process had taken a milder course as a result of a more favourable balance of intake over loss, and had spontaneously been arrested as the diarrhoea ceased. The same argument applies to potassium deficit, since cow's milk contains 1·54 g. of this electrolyte per litre and if re-alimentation is not long delayed is sufficient to supply the child's needs.

Treatment

The decision to treat these cases with large doses of protein was first taken on the supposition that fatty infiltration was the main pathological change in the liver and with the knowledge that methionine has a strong lipotropic action. Protein, it was argued, would also supply badly needed nitrogen and calories. Later, when the lesion was suspected to be of a more complex nature, justification for this form of therapy appeared even greater, since more than one of the amino-acid constituents of the protein molecule might be required (Witts, 1947).

There is some reason to believe that intravenous human serum in adequate amounts would prevent this complication of gastro-enteritis (Alexander), but regular parenteral alimentation in all cases has its restrictions and disadvantages. The oral route was favoured on general principles and casein hydrolysate chosen in the belief that it would be the most readily absorbed of any form of orally administered protein. Large amounts were given, as it had been shown that these could be taken without ill effect (Palacky, 1947). On the rare occasions where persistent vomiting precluded oral administration, casein hydrolysate was given intravenously. For various reasons this form of protein was preferred to serum. The main object was to present the liver immediately with all the essential amino-acids. If this depended on the breakdown of serum protein it was thought there would necessarily be some delay in their supply (Eckhardt et al., 1948). Nevertheless in analysing the results any serum given has been taken into account, the protein content being reckoned as 6 g. per cent., and in one case this proved highly significant.

The preparation used was ' casydrol ' (Genatosan) which the makers claim contains all essential amino-acids, with peptides in the proportion of about 40 per cent. Analysis revealed methionine in a concentration of 3 per cent. in the intravenous preparation, that is 0·075 per cent. in the solution as administered, and 1 to 2 per cent. in the oral powder, with cystine in considerable amounts. Oral ' casydrol ' consists of equal parts of hydrolysed protein and lactose. It was given diluted in water or in breast milk in concentrations up to 15 per cent. (that is 7·5 per cent. casein hydrolysate). Beginning with small amounts, the quantity of 'casydrol' was gradually increased to 60 to 80 g. a day, and the largest amount given was 120 g. a day. Breast milk was used in the belief that it is the most easily digestible, and was introduced early in most cases. Intravenous 'casydrol' was administered in 2·5 per cent. solution with 5 per cent. glucose. These sugar additions are valuable in supplying calories, sparing protein, and overcoming ketosis. Intravenous ' amigen,' which was used in one case, has the same proportions of casein hydrolysate and glucose as the intravenous preparations of ' casydrol.'

Intravenous fluid except where otherwise stated was supplied as half-strength Hartmann's solution with 5 per cent. glucose. Routine intravenous treatment in this hospital has for some time been alternate bottles of this solution and half-strength serum or plasma. Though not always regularly

followed for various reasons, it was in general applied to these cases, some of which received considerable amounts of whole protein. In the discussion which follows it is referred to as serum.

Potassium chloride was given intravenously when urgently required, as indicated by persistent fluid imbalance and low serum potassium levels. A 1 to 2 g. dose was added to the total amount of intravenous fluid given over the twenty-four hours, and this dosage was continued by mouth as soon as adequate absorption seemed likely until full feeding was established. Reference to the records shows that the intravenous route was used with caution and with frequent checks on the serum potassium. Our usual practice is to give the salt by mouth in the absence of severe vomiting or unless an intravenous has been set up to meet fluid needs. In the present series the oral route, even when relied upon from the start (Case 1) was quickly effective and quite adequate for maintenance purposes in all cases.

Extra sodium was supplied as 1/6th molar lactate, orally or intravenously, where required (Cases 2, 3, and 5).

Vitamins were administered as indicated on the records. Special importance was attached to the B-group for its possible lipotropic action (Himsworth, 1947) as well as its general value. Beminal* was chosen for injection, later replaced by Benerva† tablets by mouth.

Choline was given as an additional lipotropic agent at the suggestion of Dr. Elgood, who has since reported on its value (Elgood, 1948), but the dosage and upper limits of tolerance in human disease are unknown (Leading article, *British Medical Journal*, 1945). If a weight for weight comparison is made with experiments on growing rats, approximately 1 g. per day would be necessary to cure fatty infiltration in an infant.

Chemotherapy was employed for specific infection and on occasion empirically.

Results

All six infants recovered from the dangerous condition with which we are concerned; one died later from a septic complication. The haemorrhagic diathesis was the first to clear up in a few days; fading of the jaundice and disappearance of the oedema followed next, but it usually required some weeks before the liver returned to its normal size. Cases 1, 2, and 4 were satisfactory from the first. Recovery in Case 6 was slower, and though full investigations were not carried out and late sepsis complicated the picture, the prolonged course and failure to restore fluid balance was probably related to potassium deficiency which was not specifically corrected. Protein in this case was supplied at a rate that proved adequate in others. In two (Cases 3 and 5) the hepatic and metabolic disturbance cleared up rapidly with replacement therapy, but severe gastro-intestinal symptoms continued for some time.

Casein hydrolysate was generally well tolerated by mouth, in keeping with the experience of others (Lewes, 1944; Shohl, 1943; Hartmann et al., 1944), but the number of cases is too few to permit a final opinion on this point. It was certainly encouraging to find the digestion settling well at the height of treatment (Cases 1, 2, and 4). In Case 3 overdosage of casein hydrolysate is a possibility, and although the azotaemia (Jan. 19 to 24) was probably the result of dehydration and oliguria, the amount of protein offered (7 to 10 g. per kilo) at the time might well have proved too great a tax on the kidneys of an infant suffering from a reduced blood volume. In this patient, also, the adequate store of protein derived from intravenous serum previously given and proper correction of electrolytic balance had already begun to promote recovery before oral casein hydrolysate was started.

No previous records existed from which the optimum dosage of casein hydrolysate could be deduced: 10 g. per kilo had been estimated as the upper limit of assimilation (Elman, 1947). In our cases the result of intravenous treatment gives perhaps the clearest guide, and 1 g. per lb. per day was associated with good recovery (Case 5). With the wastage that is bound to occur in diarrhoea, the daily dosage of casein hydrolysate required by mouth is likely to be higher and more in the region of 2 to 4 g. per lb. body weight per day (Cases 1 and 2).

Complications

Except for some soreness of the buttocks, no complications occurred from oral administration of 'casydrol.' Vomiting, unless already a feature of the case, did not occur. The intravenous route on the other hand had disastrous complications. Even with careful precautions the prolonged period of slow administration of such a suitable culture medium carries the continual danger of chance bacterial contamination. Septic complications of the severest kind were encountered (Cases 5 and 6). We have since found that 1/20,000 merthiolate is an effective sterilizing agent, and no ill effects have been noted from its use.

Prognosis

The grave danger of hepatic failure in gastro-enteritis has been stressed and the good response to special treatment demonstrated. Late development of hepatic fibrosis cannot be excluded, but the return of the liver to its normal size, usually within a month of clinical recovery, makes this unlikely. No such complication has been found in the follow-up of our cases to date.

* Beminal contains 10 mg. of thiamine, 25 mg. of nicotinic acid, and 0·5 mg. of riboflavine, pyridoxine, and pantothenic acid.

† Benerva tablets contain 1 mg. of thiamine, 15 mg. of nicotinic acid, and 1 mg. of riboflavin.

Conclusion

Jaundice is an uncommon but well recognized complication of gastro-enteritis, and a very serious condition. Evidence has been produced that liver damage may arise from severe metabolic disturbances which follow acute states of nutritional failure. Extreme examples of the condition are recognized by jaundice, enlargement of the liver, and a haemorrhagic diathesis. Oedema is often present. Variations have been observed in the clinical picture, and milder forms are mentioned. Post-mortem investigations so far undertaken reveal two main pathological features: cell damage, and necrosis or fatty infiltration; but further studies are needed to elucidate the exact nature and order of events in the liver.

It is suggested that protein deprivation is chiefly responsible for the pathological changes in the liver, and the excellent clinical response obtained where it is supplied in an assimilable form is in favour of this theory. Dehydration and loss of potassium are also thought to play their part in the pathogenesis, and restoration of fluid, electrolytes, and this salt in particular is an essential part of the treatment.

Casein hydrolysate by mouth has proved an efficient method of providing the necessary protein when other forms requiring digestion were not tolerated. On occasion recourse had to be made to the intravenous route. This has the serious danger of infection, and a method has been described to prevent such an occurrence.

We are indebted to Sister Knapman and her nursing staff for their indefatigable care of these patients, for it is largely due to them that these children's lives were saved.

We should also like to thank Dr. Martin Bodian for his interpretation of the histology in the fatal cases.

Appendix: Case Histories

In the charts which follow, the line for weight is broken at the addition or removal of a splint.

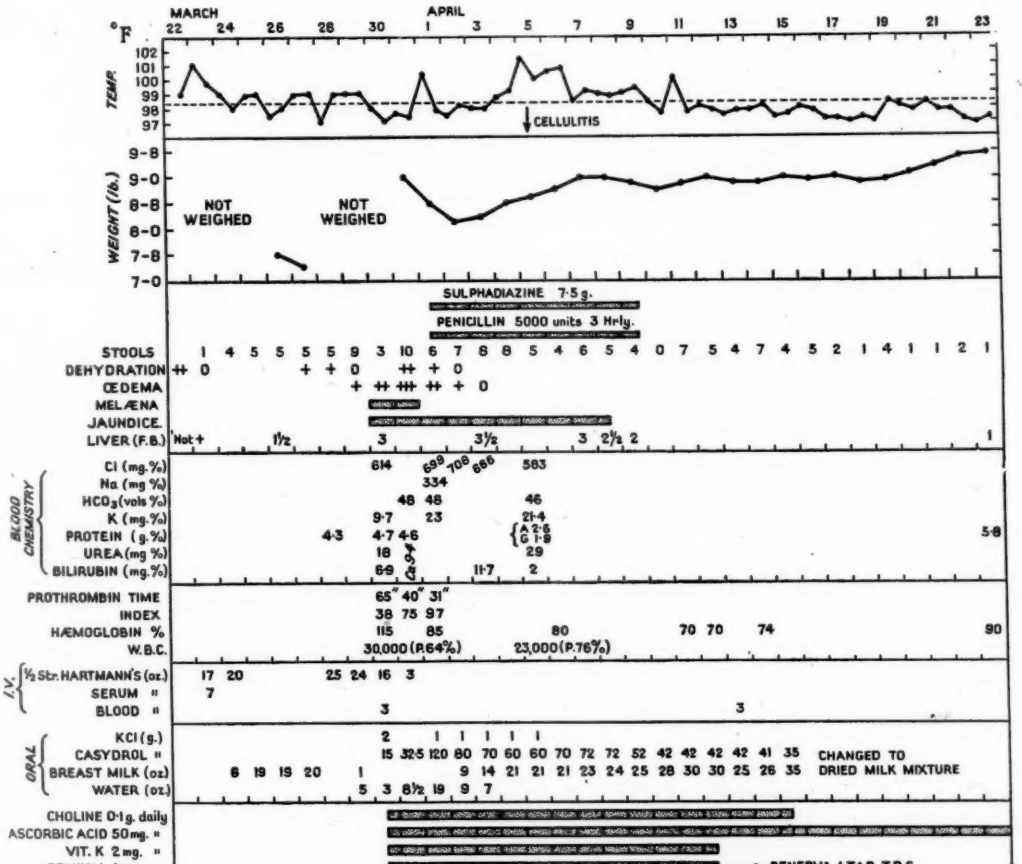

FIG. 1.—Chart of Case 1.

Chlorides are recorded as milligrammes per cent. of sodium chloride, other electrolytes, urea, and bilirubin as milligrammes per cent., serum protein as grammes per cent., and bicarbonate as volumes per cent. Haemoglobin was measured on the Haldane scale. It should be emphasized that where intravenous protein hydrolysate was given (Cases 5 and 6) the figures for dosage refer only to the hydrolysate portion of the preparation. The total daily quantity of intravenous fluid is not recorded separately, but may be obtained by adding the appropriate figures. Halibut liver oil 3 to 5 minims, ascorbic acid 25 to 50 mg. according to age, and Benerva, 1 tablet daily, was given as a routine immediately oral feeding was again well established.

Case 1 (B.M.), Aged 3 months

Gastro-enteritis, Jaundice, and Melaena: Recovery

The baby was born normally at home, the birth weight being 6 lb. and the child being breast-fed for two weeks. He did not thrive, vomited after every feed, and passed three to five stools a day, sometimes 'soupy.' On Jan. 29 he was admitted for observation, when vomiting settled in four days. The stools were two to four a day and the gain in weight was slow over a two-week period. Vomiting returned when he went home but was less, and the stools were described as 'better' though still sometimes watery. He was re-admitted on March 10 having vomited and lost 1 lb. in six days. Urine was normal. He was discharged six days later, the weight being 8 lb. Vomiting continued, and on March 20 profuse diarrhoea began. On March 22 he was re-admitted at the age of three months, dehydrated. There was no pus in the urine. Progress is recorded from that time on the chart. Vomiting was no longer a feature of the illness. Jaundice was first noticed on March 29 and lasted for ten days; melaena appeared with the jaundice but was present for two days only (fig. 1).

Comment. A child never properly nourished and with a history suggesting early feeding mismanagement developed gastro-enteritis with jaundice, melaena, and rapid enlargement of the liver ten days later. At the same time there was gross oedema and dehydration, both being corrected in forty-eight hours, and by the sixth day recovery was clearly under way. There was no infection at the relevant stage of the illness. Blood culture was negative on March 30, and myringotomy on April 2 revealed no pus. A mild relapse accounted for the infant's failure to gain weight later. The liver slowly returned to its normal size by April 23. Treatment was with oral casydrol at an average daily rate in the first week of 4 g. of protein and 35 calories per lb. Potassium chloride was also given. Breast milk was introduced on the third day of the regime. Stools improved while treatment was at its height. Chemotherapy was given empirically, though there was already evidence of general improvement.

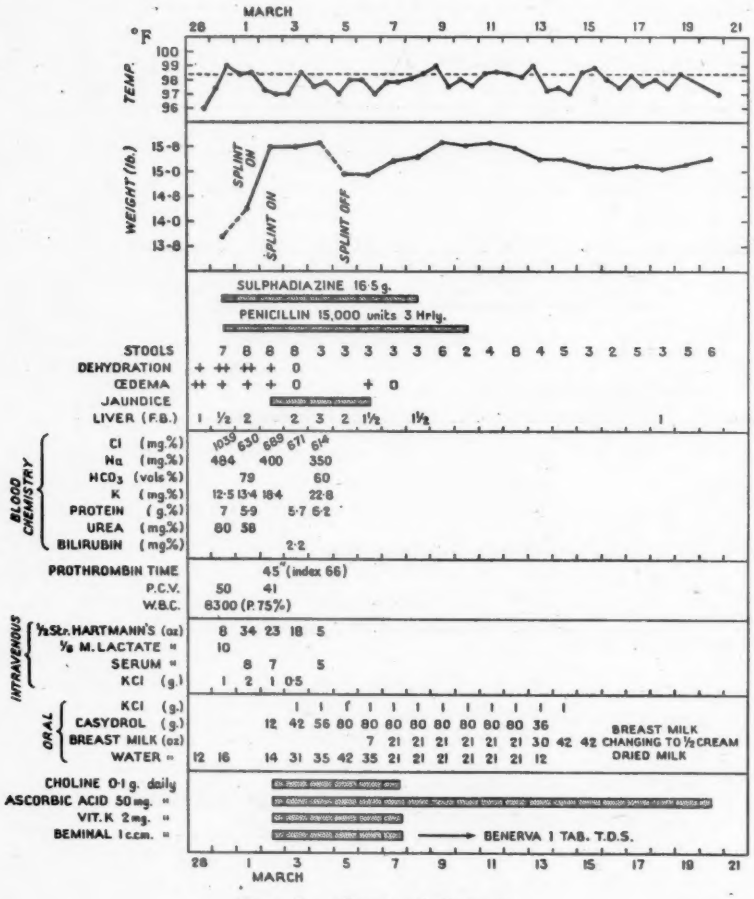

FIG. 2.—Chart of Case 2.

Case 2 (J.M.), Aged 6 months

Gastro-enteritis with Jaundice: Recovery

(Comparable in most respects to Case 1)

This child had a history of eighteen days' diarrhoea and vomiting with clear-cut onset in a nursery; he was treated at a local hospital with intravenous normal saline in considerable amounts. On admission on Feb. 28 he was in a state of mixed dehydration and peripheral and pulmonary oedema. The oedema began to subside, but dehydration became worse and on Feb. 29 an intravenous drip

was started with 300 ml. of 1/6 molar lactate and 2 g. of potassium chloride in the first twenty-four hours. Hydration rapidly improved, and crepitations and oedema disappeared. Potassium chloride was continued intravenously at the rate of 1 g. in the second twenty-four hours, and 1·5 g. in the third, and thereafter orally 1 g. per day. On March 1 the liver suddenly enlarged, from a half to two finger breadths, and the prothrombin time was 45 seconds (index 66); on March 2 jaundice developed, and on March 4 the liver increased in size down to three finger breadths. Oral 'casydrol' was given from March 2 to 6 in an average daily dose of 55 g. (equals 1·8 g. protein and 15 calories per lb.). By the intravenous route, protein was supplied as serum at the rate of 0·6 g. per lb. body weight over four days. On March 6 jaundice had gone and the liver was smaller; on March 8 it was one and a half finger breadths, and on March 18 one finger breadth. The stools quickly improved, having a good deal of substance on March 7. Breast milk was begun on that day and quickly increased. From March 9 to 11 there was a mild relapse with some watery stools. The course throughout was afebrile (fig. 2).

COMMENT. There was no focus of pyogenic infection and the urine was sterile on admission. Penicillin and sulphadiazine were given to cover the risk of possible infection from previous intravenous treatment, the wounds being very dirty, but there was no phlebitis. The absence of any haemorrhage is thought to be related to prompt treatment.

Case 3 (W.M.), Aged 5 months

GASTRO-ENTERITIS; SEVERE HAEMATEMESIS AND PURPURA; PROLONGED DIARRHOEA; RECOVERY

A healthy baby weighing 14 lb. 8 oz. developed severe enteritis fourteen days after admission to hospital for dilatation of anal stricture. On the seventh day of illness and while still on an intravenous drip he developed mild generalized oedema to which an excess fluid intake contributed. Its subsidence by the next day coincided with a deceptive appearance of general improvement which, though not apparent on the chart, was sufficient to persuade observers that he had turned the corner, and the first intravenous drip was completed with a blood transfusion. Watery diarrhoea continued, and progress is recorded on the chart from the eighth day of his illness.

A macular rash which appeared soon after admission and lasted a few days was thought to be caused by a barbiturate. The profuse watery diarrhoea was unaffected by two twenty-four-hour periods of starvation. On the thirteenth day there was bilateral suppurative otitis media, the drums

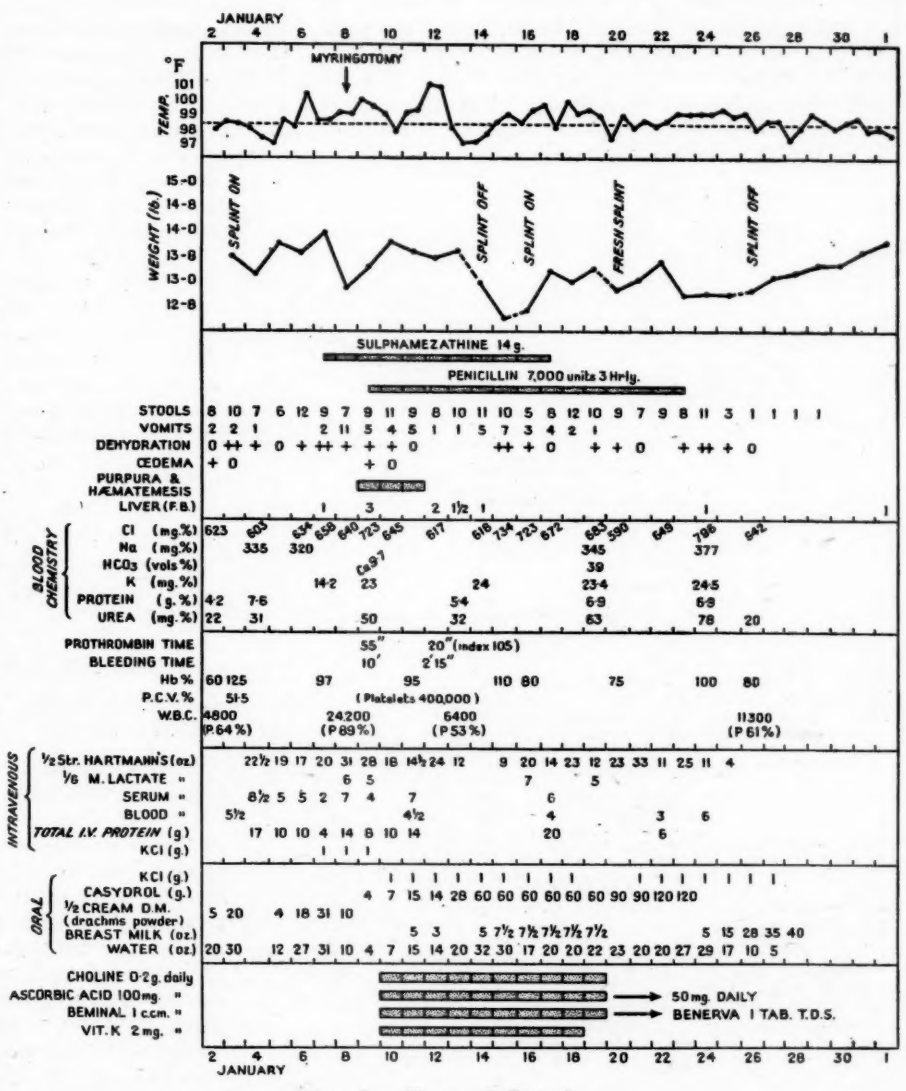

FIG. 3.—Chart of Case 3.

having been normal three days before. On the fourteenth day there was extensive purpura and haematemesis, sudden gross enlargement of the liver, and slight puffiness of the face, but no generalized oedema. Oral casydrol was begun. Intravenous treatment included potassium chloride, 1/6 molar lactate, blood, and much serum. After seventy-two hours the purpura had gone and there was no more haematemesis or melaena. The liver returned to normal size quickly, although profuse diarrhoea continued, needing further prolonged treatment. There was no jaundice. The urine was sterile (fig. 3).

COMMENT. Though initial doses of casydrol were small, the intravenous serum must be taken into account as a source of protein. In the six days before symptoms of liver damage developed, daily protein intake by mouth was at the rate of 1 g. per lb., much of which must have been lost, and 0·6 g. per lb. intravenously. In the first three days after the onset of these symptoms 0·3 g. per lb. was supplied orally as hydrolysate and 0·8 g. per lb. intravenously as serum. In this case high oral dosage of casein hydrolysate later was associated with continued diarrhoea.

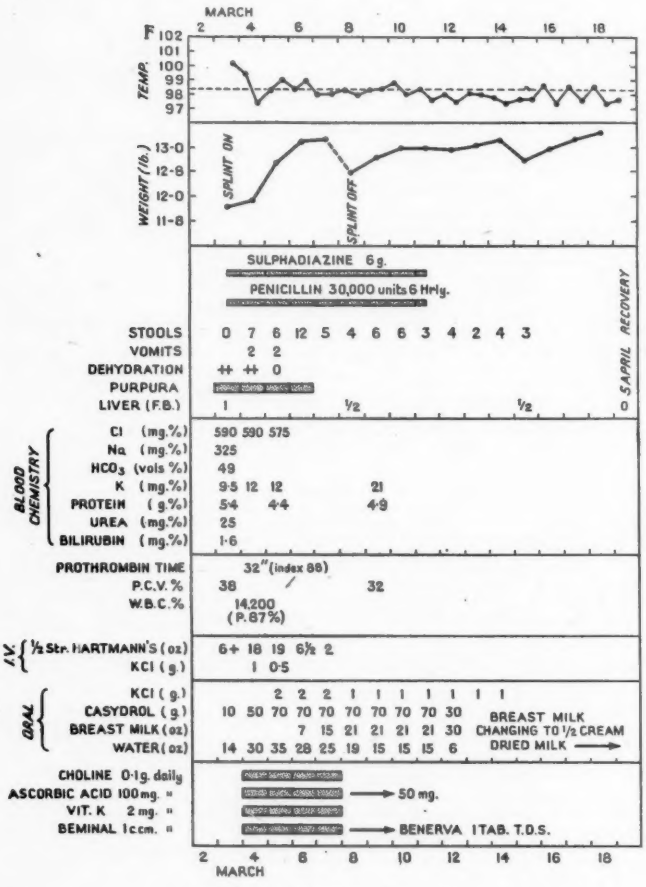

FIG. 4.—Chart of Case 4.

Case 4 (J.P.), Aged 4 months

GASTRO-ENTERITIS; SCANTY PURPURA AND LIVER ENLARGEMENT OF UNCERTAIN SIGNIFICANCE; SEVERE DEHYDRATION; RECOVERY

This baby, with a history of twenty-seven days' diarrhoea and vomiting, was treated for fourteen days in a local hospital with two three-day intravenous infusions of normal saline and a blood transfusion (no intravenous fluid was given for the last five days), and a dried milk mixture supplying an average fluid intake of 3 oz. per lb. The stools improved but hydration became inexplicably worse. On March 2 the liver was found to be palpable at one finger breadth, and it was firm; there were petechial haemorrhages on the palate, conjunctivae, and skin flexures, and also slight generalized oedema which had gone by the next day. The baby was admitted to the Hospital for Sick Children on March 3, and progress is recorded on the chart from that time. The urine was sterile. There was no focus of pyogenic infection (fig. 4).

COMMENT. This case did not present the full clinical picture described in the other five. Bleeding was confined to small haemorrhages in flexures and palate. Prothrombin index was normal. Liver enlargement was not remarkable, but did subside slightly. There was no jaundice, though serum bilirubin was raised. Serum potassium was very low. She was at the time of her transfer in a phase where hydration was obviously difficult to achieve despite a good oral intake and the development of slight oedema. Uninterrupted oral feeding throughout her period of treatment in the local hospital is noteworthy. Her state at the time of transfer is to be compared with Case 2 on Jan. 28 to 29, with Case 5 on March 7 and with Case 1 on March 29 to 30. Oral casydrol was well tolerated in large doses. Chemotherapy was given to cover the risk of a blood-stream infection from previous intravenous infusions.

Case No. 5 (R.P.), Aged 8 months

GASTRO-ENTERITIS; JAUNDICE AND HAEMORRHAGE; SEPTIC COMPLICATIONS; RECOVERY

This baby was sent to hospital for investigation of vomiting. He had a history of 'vomiting' since birth, and of passing two or three stools a day, sometimes green and slimy, from the age of five months. Some degree of mismanagement, including overfeeding, was partly responsible for these symptoms. He was weaned, vomiting ceased, and in ten days he went home weighing 17 lb., having brief pyrexia on Feb. 23 and 24. After three days he vomited, refused feeds, had offensive stools, and became collapsed. On re-admission on Feb. 29 he was having frequent effortless vomits and was put on an

intravenous drip. Progress is recorded on the chart from this time.

The first stool was virtually normal, but with resumption of oral feeds diarrhoea became profuse and watery. Haematemesis began on March 7 and jaundice with enlargement of the liver appeared soon afterwards. Vomiting was copious, and little given by mouth was retained. An attempt to combine oral feeding with intermittent gastric drainage was unsuccessful. He was given by the intravenous route casydrol 2·5 per cent. glucose 5 per cent., electrolytes, including potassium and extra saline, serum, and blood. The parenteral supply at the critical stage, March 7 to 16, was at an average daily rate of 1·2 g. of protein and 18 calories per lb. (1 g. casein hydrolysate and 0·2 g. serum per lb. body weight). Oral feeding was tried with casydrol in approximately 12 per cent. solution (6 per cent. casein hydrolysate) reduced to 3 per cent. (1·5 per cent.) and omitted after a week as dilute breast milk was introduced. On March 12 there were the first signs of left otitis media, which on March 13 yielded pus. On March 13 there was a general maculo-papular rash. On March 14 pus and B. coli were found in the urine and a blood culture grew Staphylococcus aureus. The worst of the metabolic disturbance was not over, but watery diarrhoea continued for some days, with some substance in the stool on March 17 and the first formed stool on March 21. Subsequent illness was prolonged, with the development of multiple abscesses, and on April 5 meningitis (no organisms cultured), from which recovery after treatment with penicillin and streptomycin was complete. The liver was one finger breadth on April 4 (fig. 5).

COMMENT. Jaundice, a grossly enlarged liver, and haematemesis developed after a thirteen-day illness in which vomiting of unusual severity had been a feature. At this stage there was no pyogenic infection. Evidence of liver damage regressed quickly under treatment. There were two phases of moderately severe dehydration. Oedema was present, but not gross. At first potassium was not supplied adequately. In addition a queer electrolytic disturbance developed, which has been seen since in other cases, consisting of continued loss of chloride in the urine despite low serum chloride and sodium. It may in part explain the lack of any gross oedema. No adrenal cortical extract was given. Suppurative phlebitis developed at some of the intravenous sites, and though the bottles were not cultured, there is good reason to suppose it was the result of contamination during the long period of suspension. Chemical irritation did not seem to play any part, as only a proportion of the veins used were affected.

Our thanks are due to Dr. Wilfrid Sheldon for permission to publish this case.

Case No. 6 (L.W.), Aged 1 month

GASTRO-ENTERITIS; PROLONGED JAUNDICE WITH RECOVERY; LATER DEATH FROM SEPSIS

This baby's birth weight was 7 lb. She was breast fed. She was born in a nursing home, where she had diarrhoea as part of a small epidemic. Stools 'improved' but vomiting and difficulty in feeding continued, with failure to gain weight. There was severe diarrhoea and vomiting for one week before

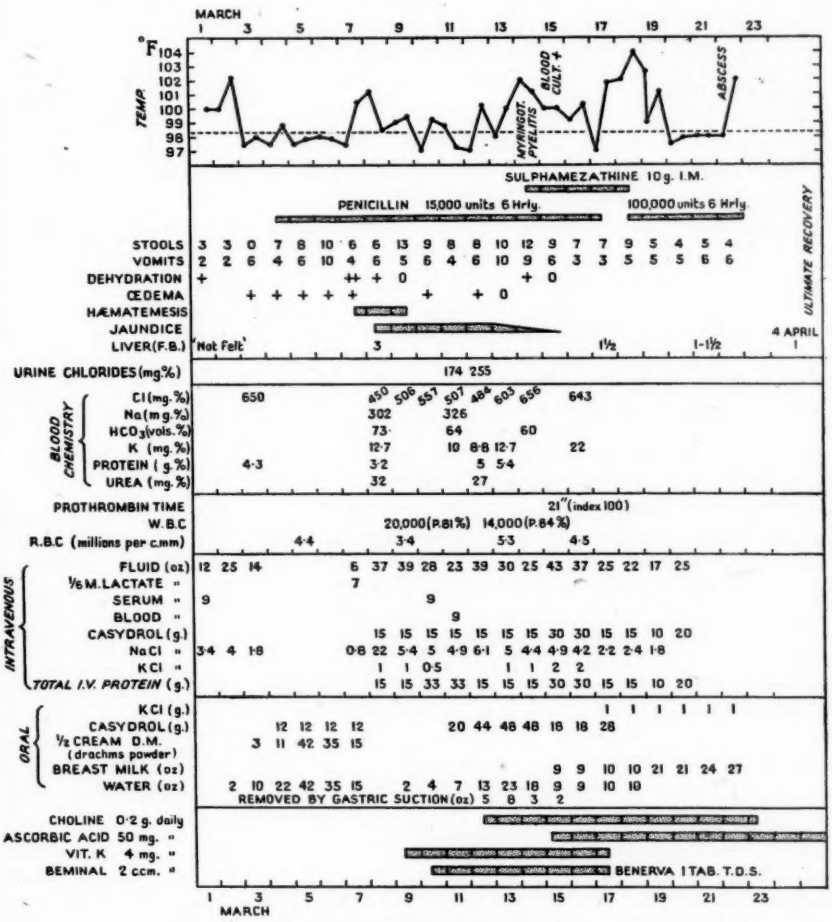

FIG. 5.—Chart of Case 5.

admission, and jaundice for two days. The urine was sterile. Progress is recorded on the chart from admission on Oct. 3, with jaundice and enlargement of the liver as marked features.

Phlebitis developed on Oct. 8 proceeding to cellulitis, with B. coli on culture, the same organism being grown from a bottle of 'amigen'. On Oct. 20 she was found to have B. coli meningitis, successfully treated with streptomycin. From about this time the stools, though frequent, were minute in quantity and semi-formed. On Nov. 8 there was a low-grade staphylococcal abscess at the site of a previous intravenous injection, and on Nov. 20 she was found dead. At autopsy an unsuspected staphylococcus lung abscess was found. Histologically the liver showed no fatty infiltration or fibrosis (fig. 6).

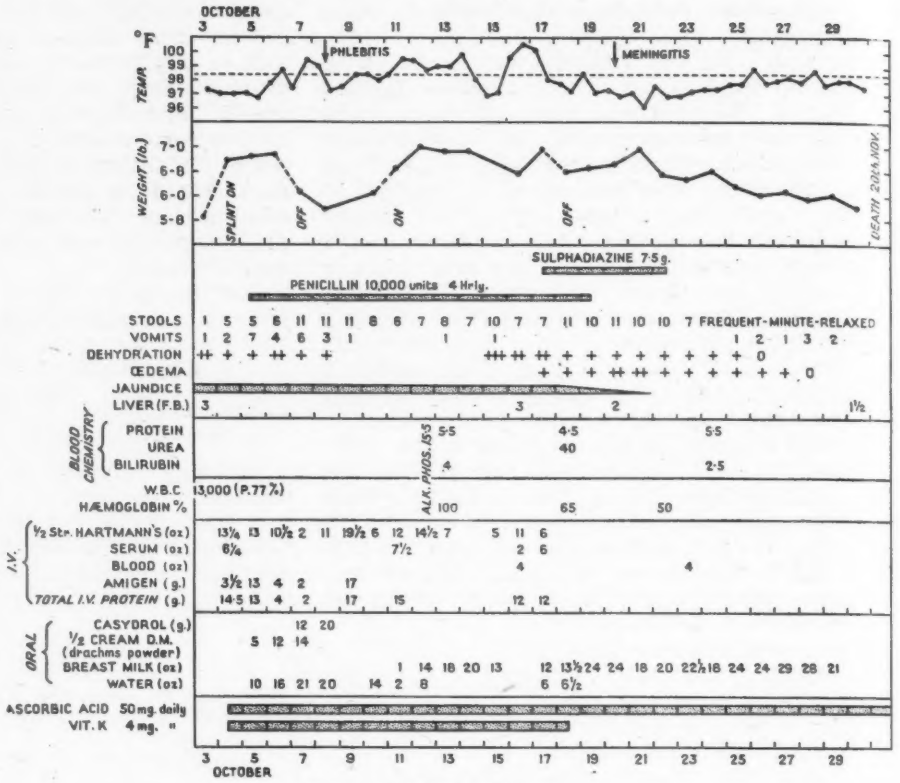

FIG. 6.—Chart of Case 6.

COMMENT. Close inquiry into the history revealed that the stools were never normal from the time of the first diarrhoea. There was no infective focus when liver symptoms developed. Signs of liver damage slowly subsided over two weeks. Protein was supplied during this time at an average daily rate of 2·1 g. per lb., of which 0·8 g. per lb. was intravenous as serum and casein hydrolysate and the rest oral, for the most part as breast milk. Severe diarrhoea continued. No extra potassium was given. Hydration was never satisfactory and, despite a fluid intake that was not excessive, pronounced oedema developed, clearing rapidly as subsidence of diarrhoea permitted resumption of normal feeding. Meningitis was a complication of treatment. Death was from a later and unrecognized similar pyaemic complication.

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SPINA BIFIDA CYSTICA

BY

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A very large number of papers on the subject of meningoceles have been published since interest became really awakened in the middle of the last century. The majority of them are accounts of a few cases of an unusual type, or of a series of cases in which a particular operative technique has been used with an apparent improvement in the results; some of the papers are reviews of a large number of cases collected from various sources, and it is from these that most of the facts showing the general course of the disorder are obtainable.

In 1905 Moore published an analysis of some two hundred and fifty articles taken from the index catalogue of the surgeon general's office; it appeared from this that the mortality was over 35 per cent. following operation within the first few months of age, but was only 4·7 per cent. if operation was delayed till the age of four or five years. He concluded that the age of infancy and the presence of complications were contra-indications to operation; that all that a surgeon could hope to accomplish was removal of the unsightly tumour, although he mentioned a few cases where clubfoot or incontinence were reported to have been improved by operation.

Dandy and Blackfan (1914) suggested that the sac acted as an absorbing surface and that its removal upset the secretory equilibrium of the cerebrospinal fluid so that hydrocephalus resulted; this idea was restated by Harmer (1920) and Cutler (1924), who devised measures to preserve the sac wall at operation, but their operative mortality remained very high. Fraser (1929) reviewed the condition in a detailed and careful paper, suggesting a classification and operative technique. Penfield (Penfield and Cone, 1932; Penfield, 1935) emphasized that he considered that the sac provided an absorbing surface for cerebrospinal fluid, and so he retained the sac at operation; he gave an operative mortality of under 10 per cent. Gross and Sachs (1934) stated that the development of hydrocephalus was not common after operation if not already present. Kolodny (1933) claimed that the operative mortality might be reduced and described sixty cases in which there were three deaths after operation, nine neurological sequelae, and no hydrocephalus. He considered that there was no proof that operation was the cause of hydrocephalus, but that it was either present previous to operation or was a consequence of infection. Harrar (1937) found the incidence of spina bifida of all types to be about 1 : 1,500, in the records of confinements at the Lying-in Hospitals, New York, and stated that the results of operation gave no encouragement to alter the opinion that operation is of no value except in simple meningocele, uncomplicated in any way.

Russell and Donald (1935) broke new ground by their demonstration of the presence of the Arnold-Chiari syndrome in a number of cases, which suggested a mechanism for the development of hydrocephalus in some instances. This paper, and that of Ingraham and Swan (1943) are really the only ones to produce any facts concerning the course of spina bifida since Moore's (1905) survey. Ingraham and Swan (1943), in a detailed survey of 546 cases of spina bifida and cranium bifidum, pointed out the weaknesses of their analysis, due both to incomplete records and to the lack of thorough post-mortem examinations. They concluded that the presence of a mass, in spina bifida, constituted an indication for operation in most cases, and that the age of choice for operation lay between twelve and eighteen months. They also considered that a progressing neurological disability was a strong argument for operation, on the grounds that growth caused increased tension on the anchored cord; and that a lipomatous growth might be pressing on the cord.

Little idea can be gained from any of the literature of the progress of any child with a specific type of meningocele which is left untouched. There is no positive evidence that a simple meningocele is harmful except in rare instances. Very few of the authors give any late results on cases that have been followed up after operation, and many fail to indicate what selection has been exercised in choosing the cases for operation. Statements showing the frequency with which the head was measured before operation are entirely missing in the discussions on hydrocephalus. It does appear, however, firstly that there is a very high mortality in spina bifida cystica in general with or without operation; secondly that operation on unselected cases is unlikely to reduce that mortality; thirdly that operation on cases of simple meningocele at any age has a low mortality and that after the age of four years it is a fairly safe procedure. Finally, there is no reliable evidence in the whole of the literature that operation has ever saved a life; nor, except for Ingraham and Swan's ten cases, any

reliable evidence that neurological symptoms have ever been relieved.

Spina Bifida

Survey of the literature shows that spina bifida cystica is sufficiently rare to make it difficult to form a large enough series from which any sound conclusions may be drawn, and yet sufficiently common to allow a number of dogmatic opinions to be formed on its course and proper treatment.

One hundred and sixty-one cases of spina bifida associated with a protruding sac have passed through the wards and out-patient departments of the Hospital for Sick Children between the years 1938 and 1947; I had hoped to find in this analysis some indication as to whether these children were benefited by operation or not, whether operation was ever in fact an emergency measure, and whether hydrocephalus was precipitated by operation. Partly because of a poor follow up, largely because essential facts were frequently missing from the notes, there is little to add to the facts already well known and described by Ingraham and Swan (1943) in their analysis.

These cases have been operated on by various surgeons whose ideas concerning the best time for operation and the best type of operation and even concerning the indications for operation are by no means the same and whose ideas may have altered during the ten years under review.

Of the 161 cases rather more than one-third are certainly living and rather more than one-third are certainly dead; of the remainder it is likely that the majority have also died. These figures, and those showing the frequency with which the sac was found in various sites, are similar to those published in other surveys (table 1). Congenital deformities of the types commonly associated with spina bifida were found in the usual proportions and call for no comment.

TABLE 1
MORTALITY IN THE PRESENT SERIES

	Total	Alive	Dead	Unknown
Cranial ..	20	11	5	4
Cervical ..	4	4	0	0
Dorsal ..	6	3	3	0
Lumbo-dorsal	9	1	4	4
Lumbar ..	69	27	25	17
Lumbo-sacral	17	9	6	2
Sacral ..	26	11	12	3
Sacro-coccygeal	1	0	1	0
Unknown ..	9	1	2	6
	161	67	58	36

Fate without operation. Seventy-four children were not operated on, and eighteen of these are known to have reached one year of age, but only ten were normal in every respect (except for the cyst) when last seen. Thirty are known to have died, mostly in the first few weeks of life, and of twenty-six the fate is unknown, but twelve of them were so grossly deformed as to make it likely that they died early, whilst only five of the remaining fourteen were without other abnormality. Thus, at most, only fifteen of the original seventy-four can have developed into normal children. Two sacs fibrosed and disappeared almost completely, leaving only a small fibrous knob, the one spontaneously and the other after rupture. It must be remembered that these figures give little direct information on the normal course of the whole group in the absence of operation, because they are formed for the most part from those cases in which operation was impossible or unlikely to be beneficial, and which, from the nature of their associated lesions, would have a bad prognosis.

Fate following operation. The cases which underwent operation form a selected group from which all the severely deformed and markedly paralysed children were excluded, so vitiating any direct comparison between the surgically treated and the remainder. Eighty-seven cases altogether were operated upon, eighty-three by excision or obliteration of the sac, three by suboccipital decompression, and one by simple incision of the sac.

Fifty-nine survived until they were at least one year old, and forty-one were living at the time of the survey, of whom thirty-one appeared to be physically and mentally normal; that is, 35 per cent. of those who underwent operation. The present series suggests that the likelihood of operative success increases after the first four weeks of life, the mortality before this age being almost double that which occurred later, and which remained more or less the same after the first month (table 2).

TABLE 2
RESULTS OF OPERATION

Age	Total	Deaths	% of total operations	% of group operations
1 month and under ..	27	14	14·9	48
6 months and under ..	28	6	6·9	21
Over 6 months ..	32	8	9	25

The assessment of the best time for operation requires consideration not only of the operative mortality at various ages, but also of the natural mortality, and it can be seen that this is greater after the first month than before (table 3).

However, the increasing death rate with age largely reflects the dying off of the inoperable cases, and it certainly cannot be concluded that the danger of death in the uncomplicated case increases with age. A knowledge of the cause of death in every case, with or without operation, would show precisely whether meningocele was a surgical emergency requiring immediate intervention, but

TABLE 3
RESULTS IN UNOPERATED CASES

Age	Total	Deaths	Deaths expressed as % of each age group
1 month and under ..	134	8	6
6 months and under ..	98	11	11
Over 6 months ..	55	10	18

this the notes lamentably fail to demonstrate. Rupture of the sac is known to have been the cause of death in only one case, but of course early operation may have prevented rupture or saved life in the case of a leaking sac in other cases. It is notable how much more frequently infection of one type or another was the cause of death in the operated cases than in the non-operated (table 4).

TABLE 4
CAUSES OF DEATH IN CASES WITH NO HYDROCEPHALUS

		No.
No operation	Meningitis	1
	Rupture of sac	1
	Not connected	1
	Inoperable	6
	Cause unknown; no gross abnormality	5
	Total	14
Operation	Meningitis	8
	Leaking wound	1
	Gastro-enteritis	3
	Post-operative collapse	2
	Encephalocele	1
	Not connected	3
	Total	18

Neurological defects. No child suffering from paralysis of limb or sphincter appears to have been relieved in any respect by operation, and in eleven cases neurological lesions were a sequel of surgery; this includes none of those who died following operation. The presence of nerve tissue was noted in thirty-two and its absence in twenty-nine of the eighty-seven operated cases. Seventeen operations were performed on children already showing neurological lesions but without evidence of hydrocephalus, and eight died; some of these were severely deformed, so the figures can hardly be a reliable guide to the results of operation in those with slighter defects (table 5).

Hydrocephalus. Forty-two cases of hydrocephalus developed before operation, and only six of these are known to have survived to the time of this survey. There are three living from the group who did not undergo operation and all are grossly deformed; of seventeen who underwent surgery eight survived for the immediate postoperative

TABLE 5
NEUROLOGICAL DEFECTS

Neurological lesions arising after operation	11 cases	(living)
Hydrocephalus arising after operation	7 „	(alive 4) (dead 3)
Operations on children with neurological lesions	17 „	(deaths 8)
Operations on children with hydrocephalus	17 „	(deaths 9)

period but only three of these are quite normal. Hence the likelihood of death after operation seems greater in hydrocephalus than in the uncomplicated case, although it cannot be said that the prognosis for the hydrocephalic is made any worse by operation.

Seven children appeared to develop hydrocephalus after operation, but it is not certain that the heads were regularly measured before operation; the age of development of hydrocephalus was scattered over the first year, with most cases manifesting themselves in the first few months, whether with or without operation. It has long been held that excision of the meningocele can directly cause hydrocephalus, and whilst there is little published evidence to show that heads have ever been regularly measured before operation, there seems to be no doubt that rapidly increasing hydrocephalus may be precipitated by operation by stimulating the production of cerebrospinal fluid in some unknown way. A remarkable example of this was the child with a small pedunculated meningocele who developed a rapidly increasing hydrocephalus after operation; after over fifty lumbar punctures this subsided and she is today a normal child. No comment can be made on the frequency with which the Arnold-Chiari syndrome was found, nor on its association with hydrocephalus, owing to the small number of times in which this condition was sought during the period covered by this survey.

Discussion

These figures suggest that operation should not be performed until after the first month of life, owing to the heavy toll of meningitis and gastro-enteritis following operation at this age; rupture of the sac has not been shown to be a frequent occurrence, and it is suggested that it does only occur in sacs with a raw, thin wall and a high tension of fluid, in children who are likely to have other gross defects (Denis Browne, personal communication). The prevention of rupture of the sac, and avoidance of infection of the cerebrospinal fluid, could be the only reasons for treating the condition as a surgical emergency. It is well known that the sac tends to toughen with age and to be protected by lipomatous growth. The balance of argument, therefore, is in favour of delaying operation.

Instead of the arrangement of spina bifida into groups according to the contents of the sac, it has

TABLE 6
HYDROCEPHALUS: AGE OF ONSET

	Birth	1-7 days	7-28 days	1-2 months	2-3 months	3-6 months	Over 6 months
Pre-operative ..	11	1	10	9	0	3	8
Post-operative ..			3		1		3

been suggested (Denis Browne, personal communication) that it might usefully be classified according to the nature of the developmental error: (1) a group with dura intact (spina bifida occulta); (2) a group with skin intact, but failure of fusion of dura (the fatty and pedunculated meningocele); (3) a group with failure of fusion of skin; (4) a group associated with hydrocephalus; (5) a group associated with failure of nerve formation; (6) a group associated with 'compression' defects such as arthogryposis and perhaps the Arnold Chiari syndrome.

(It must be noted that Coughlin (1931) states that he has confirmed Von Recklinghausen's findings of a dural defect in every case.)

It is the considered opinion of some of the surgeons at the Hospital for Sick Children that the operation is purely a cosmetic one and should be delayed until the child is old enough to survive the risks of hospital life. They would operate only on meningoceles of the pedunculated type or those with a small flat tissue paper surface (type 2).

The presence of any neurological defect would seem to be a contra-indication to operation until it can be shown in exactly which cases relief can be given, and until then the balance of argument from the literature and from the cases reviewed supports the idea that further harm rather than improvement is most likely to follow operation.

There are very few facts available concerning the development of hydrocephalus; the present series gives no information on its association with the Arnold-Chiari syndrome, nor can it be said definitely how many cases developed after operation and because of operation, nor are such facts available in the literature. The scattered distribution (table 6) of age of incidence rather suggests that operation acts only as a final stimulus in some way precipitating the rapid onset of hydrocephalus; it is in any case not invariably due to a pressure cone, nor to the Arnold Chiari syndrome. The older theory that the sac wall forms an absorbing area for lack of which hydrocephalus occurs seems highly improbable.

Conclusions

There is a remarkable lack of basic facts on which to form any judgment on the value of operation in particular instances, and on such things as the actual cause of death with or without operation; on the development of hydrocephalus; on the age of development of the Arnold-Chiari deformity.

The results of the present series, and conclusions drawn from the literature in general, would suggest that operation should be delayed until after one year of age, and should be performed only on children showing no developing hydrocephalus and no neurological abnormalities. In at least 40 per cent. of such cases there is a chance of obtaining a normal child. It is clear, however, that there is no basis in fact for supposing that operation should be performed at all, except for purely cosmetic reasons. The lump is unsightly and may greatly distress the parents and later the child himself; the advantages of removing this must be weighed against the dangers of causing paralysis of sphincters or limbs, and even the risk of death. No relief of any other disability can be expected, although it is not impossible that in rare cases a nerve may be relieved from pressure or tension and improvement obtained. In centres where a sufficient number of cases are likely to be seen it would seem important to adopt a standard line of treatment or of operative technique, accompanied by thorough recording of the physical signs.

In this way the results of conservative and operative methods may be more accurately assessed; and, if a technique is eventually evolved by which damage to nerves is prevented, its value will be readily seen.

I wish to thank the surgeons of the Hospital for Sick Children for permission to make use of their cases, and Mr. Denis Browne and Dr. Martin Bodian for their helpful criticism.

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PULMONARY COLLAPSE IN PERTUSSIS

BY

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It is recognized that whooping-cough, or as it is better termed pertussis, is a frequent cause of chronic lung disease, though the actual nature of the morbid process is not always clearly understood. Articles on bronchiectasis frequently refer to pertussis as an antecedent illness, and this is also true of many articles on catarrhal lung, chronic bronchitis, and recurrent pneumonia, occurring in children. Bronchiectasis is ascribed to pertussis in a variable percentage of cases but there is less information available as to how many cases of pertussis develop bronchiectasis. This article deals with the case histories and radiographs of forty-four children who developed pertussis and who were followed in out-patients until free from symptoms and signs or until they were lost sight of. In this way an attempt has been made to follow the respiratory complications of pertussis to resolution, or until such changes as had occurred might be considered permanent. As it is not everywhere accepted that collapse of a lobe is a common complication of pertussis, and because there is as yet no general agreement that lobar collapse is the main cause of bronchiectasis, the theoretical considerations are first reviewed.

Pertussis

Pertussis was first described by Guillaume de Baillou in 1578. He named the disease Quinta or Quintana to indicate the tendency for the bouts of coughing to recur at five-hourly intervals. Cruickshank (1942) has reviewed the epidemiology of the disease and has given the overall mortality as 1·26 per cent. with a maximum mortality in the age group 0-2 years of 3·7 per cent. In the five-year period 1943-7 notifications for England and Wales averaged 87,652 a year, and deaths 894, or a mortality of a little over 1 per cent. In hospitals the mortality is higher; the L.C.C. hospital service recorded a mortality of 8·47 per cent. for the years 1929-32, whilst the combined Glasgow hospitals recorded a mortality of 27 per cent. for the years 1931-5. In this small series the mortality was 9·1 per cent. In the years 1929-32 pertussis was the fourth major cause of death in London in the age group 0-5 years, and Dingman (1946) in the U.S.A. gives pertussis as the third major cause of death in the age group 0-2 years. Mortality apart, the morbidity of the disease is high though there are few figures available to demonstrate this. Oswald (1947) states that serious pulmonary complications are to be expected in not less than 10 per cent. of cases.

The pulmonary collapse so often associated with pertussis has been variously ascribed to the enlargement of the mediastinal glands or to the plugging of the distal small bronchi and bronchioli with viscid sputum. Engel (1947) favours enlarged glands, but Kohn et al. (1944) could find enlarged glands in only five of 154 cases, and Oswald (1947) considers that enlarged glands are rare and play little part in the production of collapse associated with pertussis. Kohn et al. (1944), Feyrter (1927), Erb (1933), and Erwin (1939) have noted blocking of the terminal bronchioli by plugs of viscid sputum at autopsy, and Pospischill (1921) recorded the presence of bronchiectasis in practically all fatal cases of pertussis. Vining (1943) considers that pertussis is liable to leave behind a prolonged cough; of one hundred children with a chronic cough, ninety-two started their symptoms before the age of 5, and in thirty-five the cough dated from an attack of pertussis. Vining (1943) and Oswald (1947) think that the main cause of such symptoms is collapse caused by blocking of the terminal bronchioli by plugs of viscid sputum. The latter author found that collapse was more common in the left than the right lower lobe, that re-expansion was unlikely after six months, and that of forty cases where the lobe failed to re-expand bronchiectasis developed in thirty-eight. Ogilvie (1941) has observed that the collapse associated with pertussis may clear after the expectoration of a quantity of sputum. Lapin (1943) considers that bronchiectasis is a common complication, and that the obstruction of the bronchial tree is maximal at the bases, giving rise to cord-like and triangular shadows on the radiograph. Harries and Mitman (1947) agree, and stress the importance of the prolonged inspiration following the bout of coughing in displacing the sputum further into the lung. Hinshaw and Schmidt (1944) think that persistence of radiographic shadows indicates incipient bronchiectasis and that they should be watched until they disappear.

Kohn et al. (1944) thought that the pulmonary complications of pertussis were due to consolidated 'atelectatic' lung, and described the radiographic

appearances in 222 children. In group one, consisting of 154 children who had little or no fever, coarse linear basal striations were seen in forty-eight, or 31·6 per cent., and consolidated lung in thirty-eight, or 24 per cent. In this group fifty-eight children were under the age of two; thirty-one had normal and twenty-seven abnormal radiographs. Ninety-six children were over the age of two, and the radiograph was normal in thirty-seven and abnormal in fifty-nine. The highest incidence of *x*-ray abnormalities was in the age group 3-5 years. In group two, children who had a fever of up to 101° F., thirteen out of fifteen, or 86·6 per cent., had abnormal radiographs. Group three, the remainder, consisted of children who had a fever of over 101° F., and forty-three of fifty-three, or 85 per cent., had abnormal radiographs. Re-expansion of collapsed areas usually occurred within fourteen days, and the majority of the collapsed areas were thought to be middle lobes.

Bronchiectasis

Collapse is probably a common complication of pertussis, and there is evidence that collapse may give rise to bronchiectasis, a condition that may be defined as any pathological dilatation of the bronchi and bronchioles beyond their normal size (Warner, 1935). Bronchiectasis was described in 1823 by Laennec, and in 1836 by Andral; both these authors commented upon its association with whooping-cough. Since then many theories have been postulated to explain the development of the disease, but until 1920 there was sufficient confusion between tuberculosis, fibroid lung, chronic pneumonia, and bronchiectasis, to render such speculations unprofitable. It is only in the last decades that the frequency of collapse and bronchiectasis has been recognized.

Louis in 1826 differentiated collapse from consolidation, and Alderson (1820), Bailey and Legendre (1846), and Gairdner (1850) commented upon the frequency of collapse in respiratory diseases. Heller in 1885 was perhaps the first to describe congenital atelectatic bronchiectasis and to provide a clear link between these two conditions. That collapse could be produced experimentally by blocking the bronchi was demonstrated by Traube in 1846, Mendelssohn in 1845, Lictheim in 1878. This has been confirmed more recently by Tannenberg and Pinner (1942), Lee-Lander and Davidson (1938), Adams and Escudero (1938), and Weinberg (1937).

The argument as to the ultimate cause of bronchiectasis still continues. Laennec (1823) thought that the dilation was due to the pressure of the retained secretions, and Andral (1836) incriminated the chronic cough, which in turn produced nutritional changes in the bronchial wall. Neither of these two theories bears close scrutiny today, though Adams and Escudero (1938), while discussing the importance of bronchial obstruction, conclude that this merely serves to dam up secretions, which produce the dilatation. They found experimentally that incomplete and not complete bronchial obstruction was associated with dilatation, a finding supported by the work of Tannenberg and Pinner (1942), and that the increased negative intra-pleural pressure associated with the collapse only affected the actual degree of dilatation and was not the basic cause. This view is difficult to uphold, and in any case complete bronchial obstruction would produce a better dam. It is unlikely that the weight of the secretions is sufficient to give rise to dilatation, and Wall and Hoyle (1932) have described cases of dry or uninfected bronchiectasis. Raymond in 1835 suggested that the strain of the constant cough would be sufficient of itself, and this view has been extended by Lemon (1926) to include the strain imposed by coughing upon a wall weakened by infection, a view supported by Thorpe (1929) and Marcy (1937). It is now agreed that the strain of inspiration and coughing is insufficient to cause dilatation unless there is a rise in intrapleural pressure from coincident lobar collapse. The bronchi are subject to atmospheric pressure on both sides of their lumen and the only variable factor is the intrapleural pressure.

Stokes in 1882 considered that the dilatation was a result of the neuromuscular paralysis of the bronchial wall secondary to infection. Corrigan in 1838 introduced the conception of traction upon the bronchial wall by fibrous tissue, a view supported by Findlay and Graham (1927). Warner (1935) disposes of fibrosis as a potential cause because dilatation is often seen without fibrosis, and because fibrosis might serve equally to compress as to dilate the bronchi. In 1843 Rilliet and Barthez had recorded a case of bronchitis that developed bronchiectasis within twenty-one days, and Perry and King (1940) consider that a collapsed lobe will always show bronchial dilatation long before fibrosis could have arisen.

The idea that hereditary influences may play a part in the causation of bronchiectasis was introduced by Hoffman, and recently Engel (1947) has gone to some lengths to produce evidence in favour of such a view. He considers that certain bronchi are constitutionally weak and are more likely to dilate. There is some evidence that vitamin deficiencies in pregnancy may lead to a maldevelopment of the finer bronchioles, and it would be premature to discard the influence of pre-natal factors altogether.

Leys (1927) writing on 'Chronic Pulmonary Catarrh,' reviews some of the literature and adds that the prevailing views at the time were either those of Laennec or of Corrigan. Leys (1927) describes chronic cough occurring after pertussis, and states that the disease lacks a name since it lacks a known etiology. In such cases he describes physical signs that might well be interpreted as those of collapse, yet he disputes the claim of Davidson that the condition is one of collapse associated with sinus infection, and he prefers to incriminate the

H. influenzae of Pfeiffer as the causal agent, a view which he has almost certainly abandoned since.

At the present time opinions are divided as to the relative importance of collapse and infection in causing bronchiectasis. McNeil et al. (1929) have described a process of acute interstitial pneumonia of the bronchi that leads to necrosis and excavation followed by relining with epithelium and dilatation. Hedblom (1931) thinks that infection weakens the wall and that then mechanical factors dilate it. The infection precedes the collapse, which is the most important mechanical factor. Moll (1932) reviews the whole subject and decides in favour of infection being the causal agent. Infection destroys the wall which is then permanently dilated, though he does suggest that the first stage is one of loss of tone that may be temporary. Bronchial obstruction favours the infection. He describes fifty-five autopsies and thirty-seven patients, and as he often noted more extensive disease at autopsy than was evident during life he concludes that the disease is capable of spread. The infective theory is upheld by Erb (1933), Boyd (1931), and Robinson (1933). This last author examined sixteen lobectomy specimens and found that collapse played no part in the production of the dilatation, but that it favoured infection. Other writers, whilst agreeing that infection is the basic cause, consider that the collapse and the increase in negative intra-pleural pressure actually cause the dilatation (Vining, 1943; Hinshaw and Schmidt, 1944; Warner, 1935 and 1934; Wearing, 1948). In their comprehensive monograph on bronchiectasis Lisa and Rosenblatt (1943) find that the one factor common to all the diseases that cause bronchiectasis is infection, and that bronchial obstruction whether partial or complete is not the basic cause.

Gairdner in 1850 had suggested that obstruction of the bronchi by sputum might produce collapse. That this is possible has been confirmed in recent years by Kohn et al. (1944), Feyrter (1927), Erwin (1939), Ogilvie (1941), Jackson (1925, 1927, 1930), Archibald and Brown (1928), Lloyd (1931), Wall and Hoyle (1932), Anspach (1943), Warner (1934), and Lee-Lander and Davidson (1938). Oswald (1947) stresses the importance of this type of collapse and also the possibility of the sputum being sucked further in during inspiration. That this is a frequent cause of collapse is now realized, and concurrently the effects of bronchial obstruction have been more accurately defined. Complete obstruction of a main bronchus leads to distal collapse, since the gas tension in venous blood is 54 mm. Hg. less than the alveolar gas tension, and the air distal to the block is slowly absorbed. In this type of obstruction there is collapse but no dilatation. Incomplete obstruction of a bronchus causes no collapse, but if the obstruction is ball valve then, depending on whether it is inlet or outlet in type, so emphysema or collapse will develop. Again there is usually no dilatation. If the obstruction is distal and many small bronchi and bronchioli are blocked, then the total anatomical effect is the same as in main bronchial obstruction, and the lobe collapses partly or totally. As a result of the collapse the intrapleural negative pressure increases and the bronchi proximal to the block are subjected to this increased force which, as the bronchi are now open to the atmosphere, dilates them. The weaker the walls from coincident infection, the more likely are they to dilate. In massive collapse the intrapleural negative pressure may reach – 423 cm. of water (Jennings, 1937). It is as well to remember that the bronchi are incapable of dilating unless they are open to the atmosphere, and this accounts for the experimental findings previously noted that incomplete and not complete main bronchial obstruction is associated with dilatation. Theoretically incomplete main bronchial obstruction is not associated with dilatation, but there is always the possibility that particles of the obstructing agent may split off, be inspired deeper into the lung, and cause multiple distal bronchial obstructions. It is interesting to observe that in lipiodol bronchograms of dilated areas alveolar filling is not seen, presumably because the terminal bronchi are always obstructed.

This leads us to a consideration of the remaining theory of origin of bronchiectasis. Collapse is common and it is often caused by plugging of the small bronchi with sputum. Lobar collapse results in an increase of the negative intrapleural pressure that is capable of causing bronchial dilatation. In fact a collapsed lobe probably always contains bronchial dilatations. If the collapsed area should re-expand before irreparable damage has been done to the bronchial wall by infection, then the dilatation may disappear; such a sequence of events would account for the cases of reversible or 'pseudo-' bronchiectasis. If the collapse is maintained, so is the dilatation; and with chronic infection superimposed the dilatation becomes permanent to such an extent that it does not disappear if the collapsed area should now re-expand. Oswald (1947) states that re-expansion of a collapsed lobe is unlikely after six months. Anspach (1933) observed forty children with bronchiectasis all of whom had triangular basal shadows on the radiographs, and he thought that the collapse was the main cause of the dilatation. Wall and Hoyle (1932) described cases of dry bronchiectasis which they thought were due to the dilating force of inspiration when the small bronchi were blocked. Anspach (1934) states that the longer the duration of the collapse the more likely is bronchiectasis to develop. Ellis (1933) describes the sequence as collapse then dilatation, and Miller (1934) quotes Schneider (1927) as saying that bronchiectasis is preceded by a purely dilated state in which there is a simple atrophy of the wall. King (1937) observed dilatation in a lobe five days after operation and discards collapse as a cause since the dilatation occurred too quickly, an occurrence that is not impossible if collapse is the cause of the dilatation. Lee-Lander and Davidson (1938), by blocking the distal bronchi, were able to

produce bronchiectasis in a cat. The degree of dilatation was less if an artificial pneumothorax was subsequently induced. In twenty patients with bronchiectasis they noted that the calibre of the bronchi varied more on inspiration and expiration than did that of a normal bronchus. Greenfield (1940) did not agree with this last finding, which Lee-Lander and Davidson had given as a point in favour of the bronchial wall being intact but dilated. Erwin (1939) supports the collapse theory and agrees that in the early stages the condition may be reversible. Andrus (1940) regards any chronic basal pneumonia as suspicious of bronchiectasis, as are increased basal striations if vascular congestion be excluded. Displacement of organs toward the diseased area occurred in 90 per cent. of cases and confirmed the association with collapse; major atelectasis, if chronic, is virtually diagnostic of bronchiectasis. He continues by saying that pneumonia regularly undergoes resolution so long as there is no collapse; if there is collapse then dilatation results from the enhanced pull of the lung. Oswald (1947) and Wearing (1948) agree, and Kornblum (1944), whilst adhering to the infective theory of origin, states that should it be demonstrated that the disease is reversible then our whole concept of the disease must be altered, presumably in favour of collapse as the main etiological agent. Wearing (1948) reports such an instance of reversible bronchiectasis but complains that the literature contains few references.

Reversible bronchiectasis. If bronchiectasis is reversible up to a certain stage in the disease process, then it is reasonable to assume that the bronchial wall has not been permanently damaged by infection and that the muscle and elastic layers are intact. Lee-Lander and Davidson (1938) have given reasons for believing that in fact the wall is intact. In some instances a collapsed area is seen to re-expand and still leave dilatation: this would be possible if, subsequent to the dilatation, infection had ensued and irreparably damaged the wall. Dilatation may be observed in a collapsed lobe or segment at an early date, before it would be possible for infection to have destroyed the wall. If infection followed by destruction is the cause of the dilatation then the condition must surely be irreversible. There are several references in the literature to reversible or 'pseudo' bronchiectasis (Erwin, 1939; Ogilvie, 1941; Moll, 1932; Robinson, 1933; Greenfield, 1940; Andrus, 1940; Kornblum, 1944). Lisa and Rosenblatt (1943) and Hinshaw and Schmidt (1944) regard such reversible dilatation as an illusion created by the temporary crowding and foreshortening of the bronchi in a collapsed lobe. Such a criticism eradicates bronchiectasis as a disease entity and can hardly be taken seriously. Oschner (1929) mentions four cases of reversible bronchiectasis but gives no details. Wearing (1948) describes one case and asks, 'How long does it take reversible bronchiectasis to become irreversible?' Oswald (1947) suggests that the time is six months. Several examples of reversible bronchiectasis have been gleaned from the literature, and a summary of these appears in table 1. Blades and Dugan (1944) discuss four other cases but give no details except that the bronchi returned to normal in three months, and they suggest that this may still happen after

TABLE 1

SURVEY OF CASES OF REVERSIBLE BRONCHIECTASIS OCCURRING IN THE LITERATURE

Year	Author	Lobe involved	Duration	Cause
1927	Findlay and Graham	1. Rt. L.L.	Less than 5 yrs.	Pertussis
		2. Rt. L.L.	Less than 3 yrs.	Pertussis
		3. Lt. L.L.	Less than 3 yrs.	Bronchopneumonia
1933	Warner and Graham	1. Rt. L.L.	Persistent, but varied with the degree of collapse	
1935	Fletcher and Dimson	1. Lt. L.L.	Less than 5 months	Measles and pneumonia
1937	Jennings	1. Lt. L.L.	1 month	
1935	Findlay	1. Rt. M. and L.L.	7–15 months	Measles
1938	Raia	1. Rt. L.L.	4 months	
		2. Rt. L.L.	6 months	
		3. Rt. M. and Lt. L.L.	Less than 3 yrs.	
1939	Wilson	1. Rt. L.L.	Less than 7 months	
1941	Fleischner	1. Lt. M. and L.L.	Indefinite	
1942	Diamond and Van Loon	1. Rt. L.L.	2 months	
		2. Lt. M. and L.L. and Rt. L.L.	2 months	
1943	Campbell et al.	1. Rt. L.L.	3 months	Atypical pneumonia
1944	Blades and Dugan	1. Lt. L.L.	9–18 weeks	
1946	Lee-Lander	1. Rt. L.L.	6–7 months	
		2. Lt. L.L.	6–7 weeks	
		3. Rt. M. and Lt. L.L.	2–15 months	
1948	Wearing	1. Lt. L.L.	4–12 months	Pneumonia

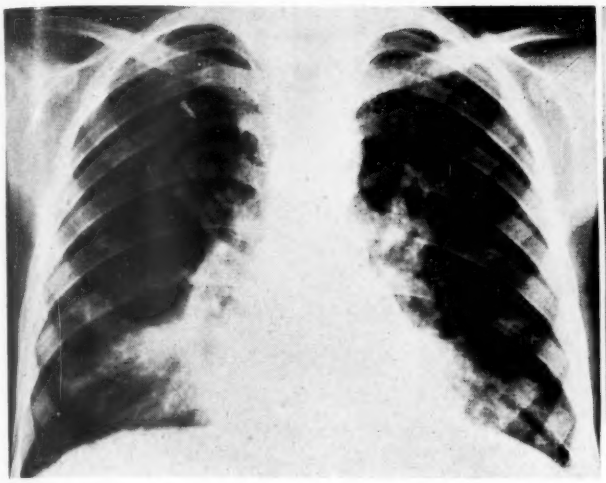

FIG. 1.

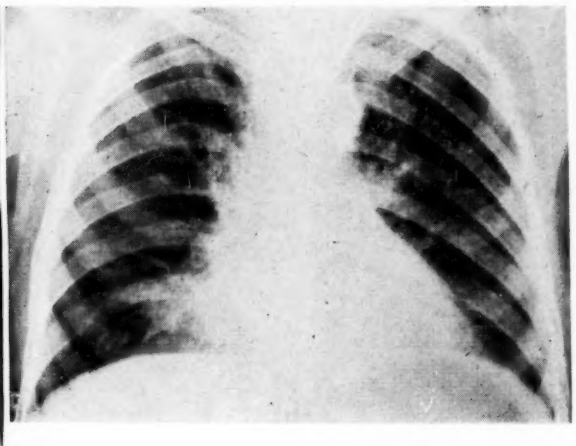

FIG. 2.

FIG. 1.—Case 6: radiograph taken on Feb. 5, 1948, of a boy aged five years. The illness was in the acute stage and there was bilateral lower and right middle lobe collapse.

FIG. 2.—The same case on March 19, 1948, showing collapse of the right middle lobe.

FIG. 3.—The same case: a bronchogram taken on April 1, 1948, showing collapse and dilatation of the right middle lobe.

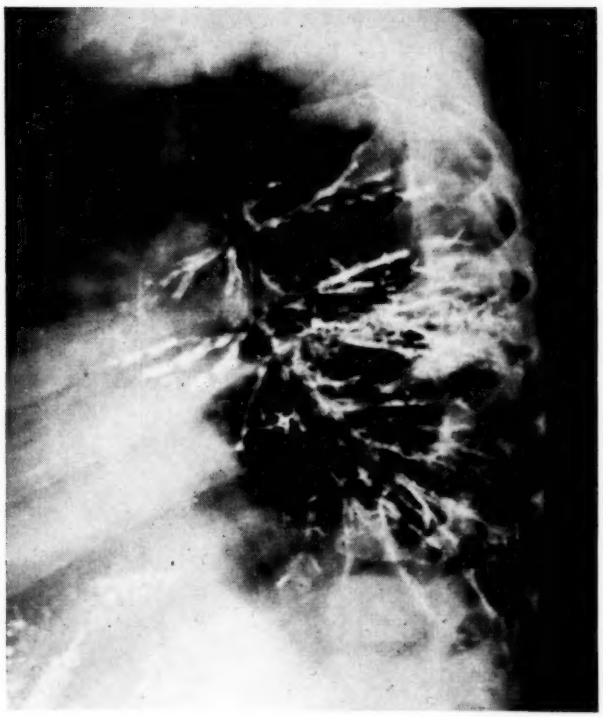

FIG. 3.

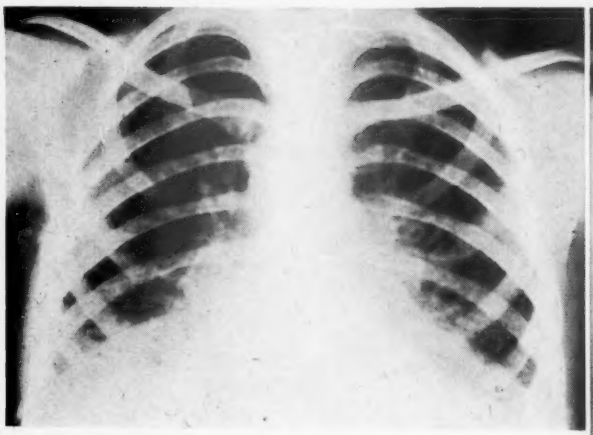

FIG. 4.

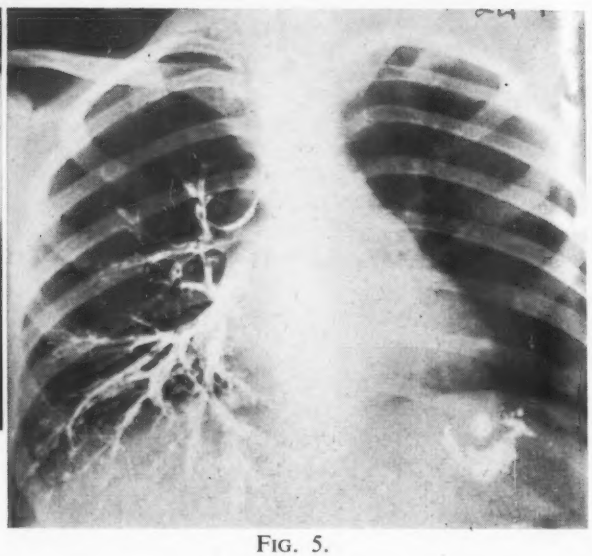

FIG. 5.

FIG. 4.—Case 11: radiograph taken on June 26, 1947, of a girl aged four years. The illness was in the acute stage and there was collapse of the right lower lobe (possibly the left as well).

FIG. 5.—Bronchogram of the same case taken on July 24, 1947, showing dilatation of the posterior basic branches of the right lower lobe.

FIG. 6.—A clear radiograph of the same case taken on Jan. 21, 1948.

FIG. 7.—Case 15: a boy aged four years. The radiograph, taken on April 17, 1947, in the acute stage, shows collapse of the left lower lobe.

FIG. 8.—The same case on March 17, 1948. Collapse of the left lower lobe is still present.

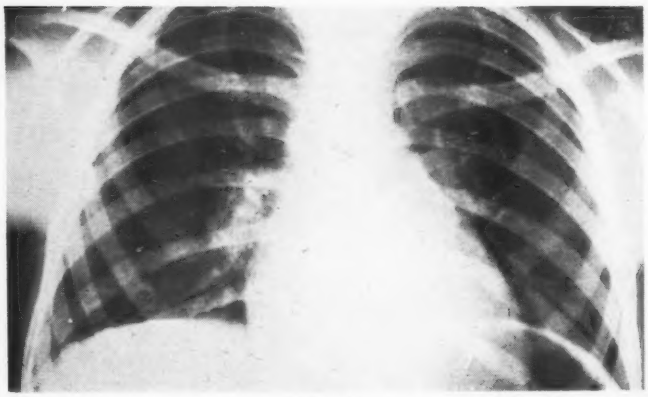

FIG. 6.

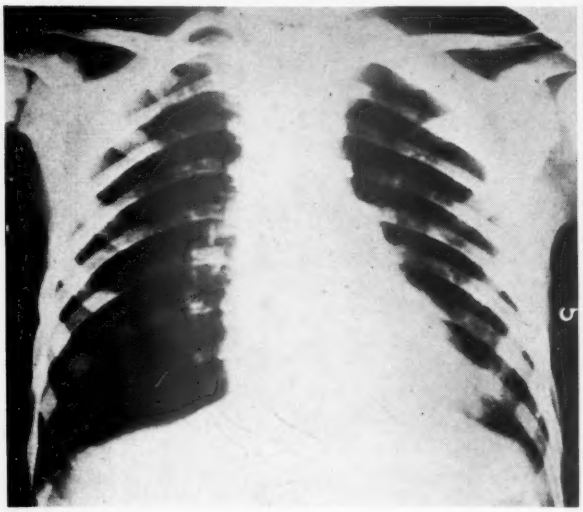

FIG. 7.

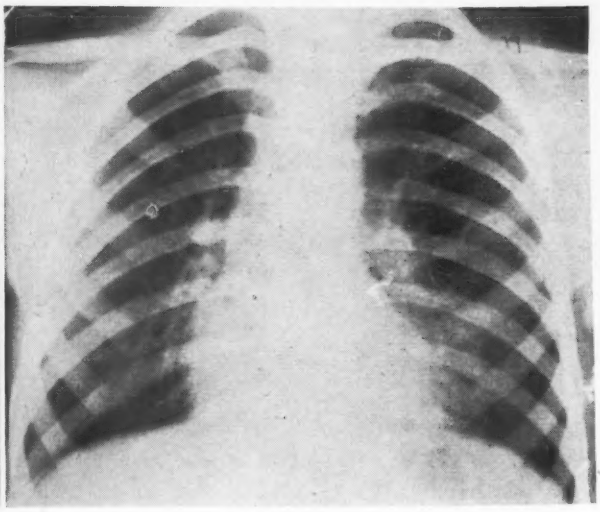

FIG. 8.

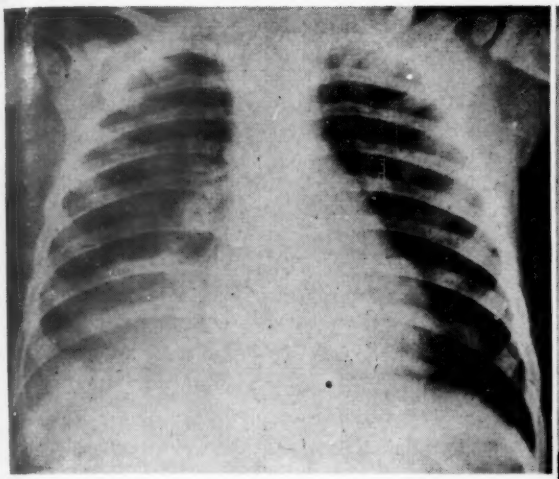

FIG. 9.—Case 19: a boy aged one year. The radiograph, taken on April 3, 1947, in the acute stage, shows collapse of the right lower lobe.

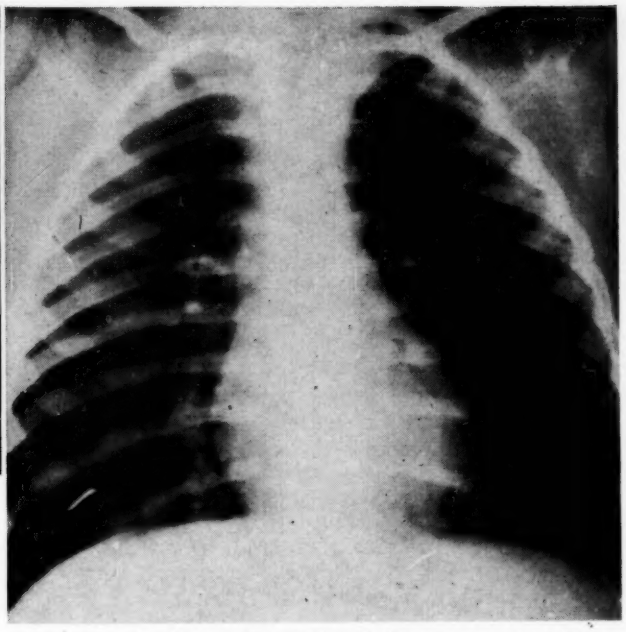

FIG. 10.—A clear radiograph of the same case taken on Feb. 25, 1948.

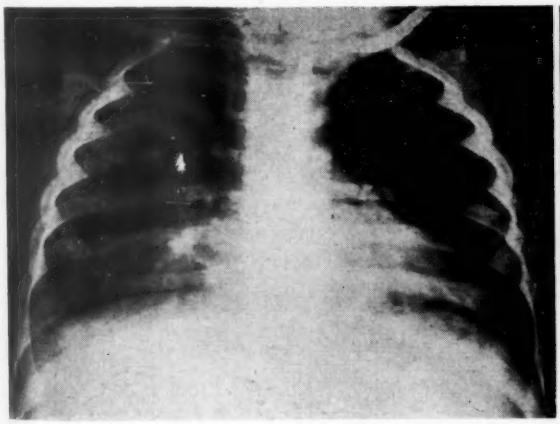

FIG. 11.—Case 7: a boy aged five years. A radiograph taken on May 2, 1947, during convalescence, showing collapse of the lower and right middle lobes.

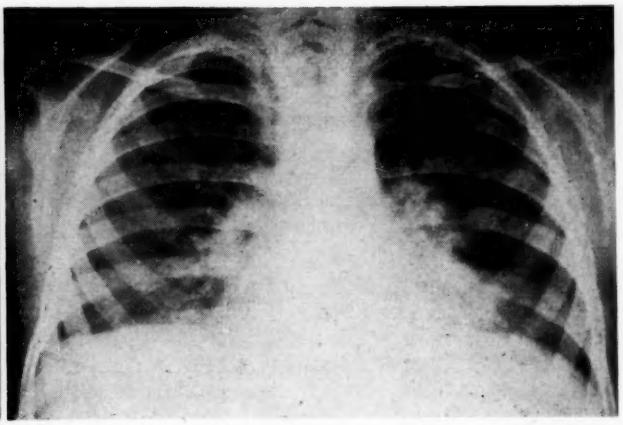

FIG. 12.—The same case on Feb. 26, 1948. The radiograph showed no change.

three months. In these examples, where a second bronchogram was done reasonably soon after the first, the dilatation had lasted roughly six months or less. This suggests that if the collapse is more permanent the dilatation becomes irreversible.

If collapse is the cause of bronchiectasis then spread of the process should not arise unless an intercurrent disease occurs that is capable of initiating further collapse. Churchill and Belsey (1939) and Perry and King (1940) consider that spread is unusual unless this should occur.

Clinical observation of cases of postoperative massive collapse lends further support to the view that viscid sputum may lead to blocking of the bronchi and collapse (Pasteur, 1908, 1914; Bradford, 1918; Briscoe, 1914, 1919; Sante, 1927; Findlay, 1932; Scott, 1925; Elliot and Dingley, 1914; Corrylos and Birnbaum, 1928).

Anatomy. A detailed knowledge of the anatomy of the bronchi is important if the full effects of bronchial obstruction are to be understood. The anatomy of the bronchi has been described by Ewart (1889), Kramer and Glass (1932), Neil et al. (1937a and b), Nelson (1934), and more recently by Brock (1942-3-4) and Foster-Carter (1942). The size of the bronchi has been estimated by Engel (1947) and Miller (1947). The diameter of the bronchi at birth is given as 5·7 mm. in the coronal, and 6·0 mm. in the sagittal plane. By adult life these measurements are 16·5 mm., and 14·4 mm. respectively. The terminal bronchioles measure 0·12 mm. at three months and 0·20 mm. in diameter by adult life. Kohn and others (1944) found that in pertussis respiratory complications were most frequent in the age group 3-5 years. If size alone were the only consideration then it would be expected that the bronchi of infants would be blocked more frequently. This does not appear to be so, and it may be that the bronchial glands, which are immature at birth, are incapable of secreting sufficient mucus until early childhood. In childhood the goblet cells are well developed but they are never present in bronchi with a diameter of less than 0·4 mm.

Radiography. Ewart in 1889 introduced the idea of constant broncho-pulmonary segments, areas composed of a framework of small bronchi whose trunk is an offshoot of a lobar bronchus. This conception has been amplified by Kramer and Glass (1932) and Foster-Carter and Hoyle (1945). Collapse of a broncho-pulmonary segment throws a shadow on the radiograph that is relatively constant, and with the aid of lateral views the area may be defined. Interpretation of radiographs plays an important part in the control and assessment of cases of pertussis. It has been assumed that the triangular basal shadows so frequently seen on radiography represent collapsed lower lobes. In the past these shadows have been variously interpreted as indicating pneumonia, mediastinal pleurisy, or fibrosis. In 1926 Singer and Graham noted that these shadows were often associated with bronchiectasis, and at operation they found that the lower lobes were collapsed. This has been confirmed by Warner (1935), Warner and Graham (1933), Ogilvie (1941), Riggins (1941), Findlay (1935), Anspach (1934), and Andrus (1940), and it has been observed that in these cases the distal small bronchi are often plugged with sputum (Anspach, 1939; Warner and Graham, 1933). Triangular basal shadows were noted in 6 per cent. of cases of bronchiectasis by Warner and Graham (1933), in twenty-seven of sixty-eight cases by Ogilvie (1941), and in 17 per cent. of cases by Joress and Robins (1944). If the collapse is lobar then compensatory emphysema of the adjacent healthy lung, and mediastinal shift, occur.

Relation of Pertussis to Bronchiectasis

Articles on bronchiectasis often refer to pertussis as an antecedent and causal illness. Table 2 gives a list of such references with the percentage incidence given, pertussis being an antecedent illness in an average of 14 per cent. of cases.

TABLE 2

ARTICLES ON BRONCHIECTASIS REFERRING TO PERTUSSIS AS AN ANTECEDENT ILLNESS

Authors	Per cent. of cases affected
Warner (1935)	4
Diamond and van Loon (1942)	8
Thorpe (1929)	26
Raia (1938)	21
Perry and King (1940)	9
Oswald (1947)	14
Ogilvie (1941)	8
Lemon (1926)	46
Moll (1932)	9
Joress and Robins (1944)	8
Hedblom (1931)	9
Graham et al. (1935)	11
Findlay and Graham (1927)	9
Boyd (1931)	9
Average	14

In this discussion it has become evident that collapse is a common complication of respiratory diseases, and that it is almost certainly the forerunner if not the actual cause of bronchial dilatation.

In uncomplicated pertussis with few or no signs of secondary respiratory infection the radiograph is often normal and enlargement of the mediastinal glands is not seen. If such glandular enlargement is seen it is highly suspicious of a coincident primary tuberculous infection. If there are signs and symptoms of secondary infection of the respiratory tract, then abnormal x-ray shadows become increasingly frequent. The abnormal shadow is often typical of lobar or segmental collapse. Clinically the physical signs usually support such a

diagnosis, and as a rule neither the signs nor the radiographic appearances respond to chemotherapy in the manner of a classical lobar or bronchopneumonia, a fact borne out by the investigation of Kohn, Rubin, and Hobart (1940). Pyrexia and cough tend to continue until the radiograph is clear, and it is probable that the majority of respiratory complications in pertussis are due to lobar or segmental collapse. Collapse will be more likely if there is secondary infection and excess secretion of mucus, particles of which tend to be inspired deeper into the lung and to block the small bronchi and bronchioli. The collapse is due to the blocking of the terminal bronchi, and this was evident in three of the autopsies in this series. The alveoli become airless, the lobe diminishes in size, the negative intrapleural pressure increases, and the bronchi proximal to the block undergo compensatory dilatation; this is reversible in the first instance but becomes permanent if the area fails to re-expand or if infection supervenes. If the collapsed area should re-expand then the dilatation may disappear. After six months or so this becomes increasingly unlikely, and such a possibility probably depends upon the degree of infection present.

Present Investigation

The present series consists of forty-four children suffering from pertussis who were in most instances sufficiently ill to warrant admission to hospital. There were twenty-three girls and twenty-one boys. The duration of symptoms before admission was less than one week in thirteen, or 29·5 per cent., and more than one week in thirty-one, or 70·5 per cent. The age incidence is shown in table 3. This

TABLE 3
AGE INCIDENCE IN FORTY-FOUR CHILDREN WITH PERTUSSIS ADMITTED TO HOSPITAL

	0–6 mths.	6–12 mths.	1–2 yrs.	2–3 yrs.	3–4 yrs.	4–5 yrs.	5–8 yrs.
No.	8	4	5	9	5	7	6
deaths	1	0	0	1	2	0	0

gives an overall mortality of 9·1 per cent. During their stay in hospital, and subsequently as outpatients these children were examined frequently both clinically and by radiograph. Five children, or 11·4 per cent. (three boys and two girls) revealed no x-ray abnormality at any time. The rest had at some time abnormal signs both physically and radiographically. It is, of course, possible that some transient radiographic changes occurred unnoticed.

The shadows seen on the radiographs were usually typical of lobar or segmental collapse, mainly of the middle and lower lobes. Evidence in favour of the shadows representing collapsed lobe was as follows: (1) physical signs of collapse and lack of response to chemotherapy; (2) association of mediastinal shift and compensatory emphysema; (3) the presence in some radiographs of visibly dilated bronchi in the shadow; (4) the similarity of the shadows with the triangular basal shadows previously discussed.

As far as possible the children were divided into three groups. Group one was composed of mild cases with few or no signs of respiratory infection and little or no pyrexia. Group two, cases of moderate severity with signs of secondary infection and pyrexia of up to 101° F. Group three, severe with marked signs of secondary infection and pyrexia of over 101° F., and a prolonged course to recovery. Four children died, and all were classified as severe cases. Case 13, a girl aged two, showed collapse of both lower and the right middle lobes on radiography, and this was confirmed at autopsy when the distal small bronchi were seen to be blocked by plugs of sputum. A similar state of affairs was seen in a girl aged three, Case 23, who in life showed bilateral lower-lobe collapse, which was confirmed at autopsy, and in Case 26, a boy aged seven weeks, who had shown bilateral lower-lobe collapse as well. Case 31, a girl aged three, died soon after admission and autopsy revealed an extensive bilateral bronchopneumonia. Four cases were mild, sixteen, or 36·4 per cent. were classified as moderate, and twenty-four, or 54·5 per cent., as severe (table 4).

TABLE 4
DEGREE OF SEVERITY IN THE PRESENT SERIES

Age	No.	Mild	Moderate	Severe	Deaths
0–6 mths.	8	1	4	3	1
6–12 ,,	4	0	3	1	0
1–2 yrs.	5	0	1	4	0
2–3 ,,	9	2	2	5	1
3–4 ,,	5	0	2	3	2
4–5 ,,	7	1	3	3	0
5–8 ,,	6	0	1	5	0
Total	44	4	16	24	4

There was no evidence of collapse in one out of four mild cases, three out of sixteen moderate cases, and one out of twenty-four severe cases; on the other hand collapse of over two months' duration was seen in one out of four mild cases, nine out of sixteen moderate cases, and thirteen out of seventeen severe cases, that were followed for a sufficient length of time. The collapse was bilateral in eighteen: the right upper lobe was involved once, the right middle lobe ten times, the right lower lobe thirty-five times, the left lingula five times, and the left lower lobe nineteen times. This preponderance of right- over left-sided collapse is unusual, though it will be appreciated that left lower-lobe collapse is more difficult to diagnose. Oswald (1947) noted left lower-lobe collapse twenty-eight times to eighteen times on the right, Diamond and Van Loon (1942) an incidence of fifteen to twelve, and Campbell

et al. (1943) an equal incidence in seventy-eight cases. The reasons offered for the greater frequency of left-sided collapse are that the left main bronchus arises at a more acute angle and that it is in intimate relationship with the arch of the aorta and the pulmonary artery. From the foregoing theoretical considerations it would be expected that collapse would have an equal incidence on both sides, and it is difficult to explain this apparent anomaly.

TABLE 5
INCIDENCE OF COLLAPSE IN PRESENT SERIES

Age	Collapse of over two months	No collapse
0– 6 mths.	2 out of 7	2 out of 8
6–12 ,,	2 out of 4	2 out of 4
1–2 yrs.	2 out of 3	0 out of 5
2–3 ,,	4 out of 8	1 out of 9
3–4 ,,	2 out of 3	0 out of 5
4–5 ,,	7 out of 7	0 out of 7
5–8 ,,	4 out of 6	0 out of 6

Collapse of a serious nature seems to be more frequent in childhood than in infancy, a fact corroborated by Kohn et al. (1944). In all collapse occurred in thirty-nine out of forty-four cases, a high incidence (table 5).

Lee-Lander (1936) says that in the collapse following the infectious fevers no prognosis can be given since our knowledge of the condition is insufficient. The duration of the collapse varies; the more severe examples tend to last longer. Of the cases that were followed until clear or for longer than a year, thirty-five of forty-eight collapsed lobes had re-expanded within nine months; thereafter no further re-expansion was seen during the time of observation. It is probable that no further re-expansion will occur after nine months; the collapse is now permanent and dilatation established. Thirty-three children were followed for more than one year, and seven still had a collapsed lobe. If bronchiectasis is a possible end result in 21 per cent. of cases of severe pertussis then treatment must be started early. Only three out of fourteen cases admitted in the first week of the disease developed serious pulmonary complications, whereas nineteen out of twenty-seven cases admitted after the first week developed such complications.

Treatment. The early diagnosis of pertussis is difficult, and in any case there is no specific treatment. Aerosporin, a new drug, is obtained from the B. Aerosporus, and it will inhibit H. Pertussis in a minimal dilution of 0·04 μg per ml. (Ainsworth and others, 1947; Brownlee and Bushby, 1948). In some cases in this series Swift (1948) gave 0·8 mg. per kg. four-hourly, and from his series he concluded that a response was usual within twenty-four hours, but that the ultimate benefit seemed to depend on the duration of symptoms before the start of treatment rather than upon the severity of the disease itself. If aerosporin is given before secondary infection has caused collapse then the pulmonary complications might be averted, though in this series the small number of cases who had aerosporin differed in no way from the others. Excluding specific treatment, sulphonamides and/or penicillin should be given to avert or reduce secondary infection, and such measures may prevent further collapse. In a few cases inhalations of penicillin were tried, using either a 'Deedon' or 'Aerosol' inhaler and a mixture of carbon dioxide and oxygen. Results were unsatisfactory as children do not tolerate a mask or tent well, but further trials would be justified.

If collapse is still present after the acute stage is over further treatment is imperative, and should be directed at the collapsed lobe. Postural drainage in the appropriate position should be given (Nelson, 1934), and this should be combined with percussion over the affected lobe in an attempt to induce the child to cough up the particles of sputum. Treatment in this manner can be given several times a day and must be given until all hope of re-expansion is abandoned, after six or nine months. It may even be continued at home under the guidance of the parents.

It will be seen from fig. 13 that the likelihood of re-expansion becomes less after six months, and

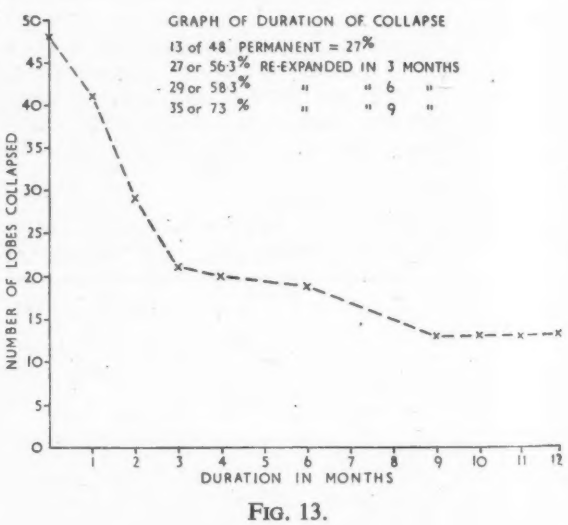
GRAPH OF DURATION OF COLLAPSE
13 of 48 PERMANENT = 27%
27 or 56·3% RE-EXPANDED IN 3 MONTHS
29 or 58·3% " " 6 "
35 or 73 % " " 9 "
NUMBER OF LOBES COLLAPSED
DURATION IN MONTHS

FIG. 13.

improbable after nine months. After this time it can be assumed that collapse is established and that bronchial dilatation is likely to be permanent. In such cases clinical symptoms of infected bronchiectasis may occur, with cough and productive sputum. If this state of affairs continues the need for surgery may arise, and at this stage complete bilateral bronchograms must be done to define the extent of the bronchial dilatations. In this series bronchograms were done on three children. Case 6, a boy aged five years, had collapse of both lower

lobes and the right middle lobe. After ten weeks the middle lobe was still collapsed and a bronchogram showed dilatation and crowding of the middle lobe branches (fig. 3). Case 11, a girl aged four years, had a collapsed right lower lobe; after three weeks this had not completely re-expanded and a bronchogram revealed dilatation of the posterior basic branches (fig. 5). Subsequently the lobe re-expanded completely. Case 36, a girl aged four years, had bilateral basal collapse that cleared in eight weeks; a subsequent bronchogram was normal.

Following an attack of pertussis a child may continue to suffer from cough, which may be paroxysmal, and attacks of bronchitis. The examination and radiograph of these children usually reveals a collapsed lobe. If treatment is inadequate and fails to produce re-expansion, the cough continues and eventually may merge with the symptoms of bronchiectasis. Many of these cases still go unrecognized, and all too often the treatment consists of an ineffective cough mixture.

Summary

The literature relating to pertussis and bronchiectasis has been reviewed. It has been concluded that pulmonary collapse is a common feature of pertussis, and that if re-expansion does not occur within nine months it is unlikely to do so, and bronchiectasis may supervene. Treatment of these cases must be prolonged and efficient. Post-pertussis pulmonary collapse is often still unrecognized.

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AROBON IN THE TREATMENT OF INFANTILE GASTRO-ENTERITIS: A CLINICAL TRIAL

BY

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In recent years a new therapeutic agent, 'arobon,' has been used in Spain, Switzerland, and other continental countries in the treatment of gastro-intestinal disorders in infants. Arobon is a powder prepared from the bean of the carob tree, Ceratonia Siliqua, which grows abundantly on the shores of the Mediterranean.

During the Spanish Civil War Professor Ramos (1941) noticed that the children of the poor in Barcelona who ate large quantities of carob bean tended to constipation and also were less subject to gastro-enteritis than were the better fed. This led him to use the roasted pulp of the bean mixed with starch in the treatment of gastro-enteritis, and with this mixture he claimed good results. Similar trials were carried out by Rozalen Sales (1942) and by Anton (1943).

Following these results Messrs. Nestlé Ltd., in Switzerland, marketed a product of the carob bean mixed with starch and cocoa under the name of 'Arobon,' and this has since been used in several continental countries in the treatment of gastro-enteritis and other intestinal disorders with much reported success.

Composition and Properties

Arobon is a brown coffee-coloured powder, made up of carob bean flour 85 per cent., starch 10 per cent., and cocoa 5 per cent. It has the following composition (Nestlé):

	%		%
Fat	1·5	Pectin	1·5
Proteins	4·5	Cellulose	6·0
Soluble carbohydrates	45·0	Lignin	21·0
Starch	13·5	Hemi-cellulose	
Mineral salts	3·5	Moisture	3·5

100 g. = 270 calories

It is very simply prepared for use by adding the powder to boiling water in 5 per cent. or 10 per cent. strength and adding a saccharine tablet to sweeten. This makes a thin suspension very similar to broth in consistency with a taste resembling cocoa.

The action of arobon in gastro-enteritis is due to its high powers of adsorption and also perhaps to mild astringent properties. By virtue of its pectin and lignin content it is said to adsorb fluid and toxic substances in the intestinal tract, and also by the bulky bolus so formed to slow down intestinal peristalsis (Martin du Pan, 1945a). Pectin forms the basis of the apple diet treatment which has been extensively used in gastro-enteritis, and lignin is an allied substance with much greater adsorptive powers. Martin du Pan carried out several experiments on the adsorptive powers of arobon and found that a 5 per cent. suspension in an 8 per cent. solution of proteins adsorbed 30 per cent. of the proteins.

Arobon given by mouth in 5 per cent. or 10 per cent. strength changes the character of the stools within forty-eight hours; they become homogeneous, dark brown in colour, and paste-like in consistency.

Previous Clinical Trials

Various workers in Switzerland and France have reported trials of arobon for gastro-enteritis in infants and older children. The method of its use has been roughly the same in all cases. Arobon in water only, in 5 per cent. or 10 per cent. suspension, is given by mouth for the first twenty-four to forty-eight hours, followed by the slow addition of some form of milk food in slowly increasing quantities. Most workers employed intravenous infusion as well when necessary and also chemotherapy in the control of parenteral infection. The arobon is continued for about ten days, by which time the infant is on full strength feeds, and the arobon is then stopped. An acidified milk, such as 'Eledon' (Nestlé) was often used in the re-establishment of feeds.

From Switzerland, Martin du Pan (1945b) reports its use on fifty-nine cases of varying severity of gastro-enteritis and on six cases of coeliac disease. All his cases were over ten months of age, and he claimed very good results. In twenty cases of gastro-enteritis in which he analyses results in comparison with twenty similar cases treated with apple diet, the stools on arobon became 'normal' in an average of 2·25 days, and complete cure was effected in an average of 3·6 days, while in the control series on apple diet the figures were 4·7 and 6·2 days respectively.

Favier (1946) treated one hundred infants under six months of age with good results. He concludes: 'The introduction of carob flour to the dietetics of small infants represents a decided step forward.

TABLE 1
CASES TREATED WITH AROBON

No.	Age (mths.)	Parenteral infection	Intravenous infusion	Chemotherapy	Total days in hospital	Days till stools 4 per day	Days on arobon
1	2	—	—	—	20	1	9
2	2	—	—	—	11	1	4
3	3	—	—	—	17	5	8
4	4	—	—	—	13	1	5
5	12	Thrush .. Otitis media ..	—	—	10	4	8
6	1	Skin infection	—	Sulphadiazine and Penicillin	31	20	10
7	6	Upper respiratory infection ..	Yes	Sulphadiazine	30	17	12
8	2	,, ..	—	,,	27	3	7
9	2	,,	Yes	,,	14	2	10
10	4	,, ..	Yes	,,	15	6	8
11	8	,, ..	Yes	Sulphadiazine and Penicillin	17	11	5
12	4	,, ..	—	Sulphadiazine	26	9	5
13	6	Thrush and Tonsillitis ..	—	Sulphadiazine and Penicillin	23	7	5
14	4	Otitis media ..	—	Sulphadiazine	11	2	8
15	4	,, ..	—	,,	18	8	7
16	1	,, ..	Yes	,,	15	5	10
17	5	,, ..	—	,,	11	2	5
18	12	Thrush and Skin infection	Yes	Sulphadiazine and Penicillin	29	10	15
19	6	Otitis media ..	—	Sulphadiazine	12	3	5
20	10	Otitis media ..	—	,,	35	24	6
21	1	,, ..	—	,,	37	14	11+16
22	1	,, ..	Yes	,,	27	10	10+7
23	5	,, ..	—	,,	9	1	8

Results are especially striking in cases of acute gastro-enteritis'. He observes that arobon was not always well tolerated and was sometimes vomited.

Similar good results were obtained by Neyroud (1946) on eighty-one cases of gastro-enteritis of various ages, and by Nicod (1947) on forty-six young infants; the latter author states: 'The diarrhoeic character of the stools disappears more rapidly with arobon, and improvement of the general condition is quicker and more constant'. Nicod also treated milder cases of intestinal upset by adding arobon to their usual feeds.

All these reports agree that arobon is most successful in cases of primary gastro-enteritis, but that its action in controlling the stools is much slower when parenteral infection is present.

Boussardon (1947) in France reports its use on sixty-eight infants between the ages of seventeen days and fourteen months. He divides his cases into three categories: simple primary gastro-enteritis, of which there were only four cases and in which arobon gave good results; thirty-eight cases with parenteral infection, in which he found that control of the primary infection was necessary before cure occurred; and severe cases with 'toxic syndrome', in which he concludes that arobon exerts no influence on the general condition but is a useful adjunct to other forms of treatment by its control of the stools. He considers that arobon is a valuable addition to the treatment of infantile gastro-enteritis, and in general its use enables a quicker resumption of feeding.

Present Trial

In view of these favourable reports a clinical trial was instituted at the Hospital for Sick Children on infants admitted to the gastro-enteritis unit over a period of six months. The general standard method of treatment was continued, but arobon was added in alternate cases, the others serving as controls. The results obtained in the 'trial' and 'control' series were then compared.

The standard method of treatment consists of stopping all feeds by mouth for twenty-four hours and substituting half-strength Hartmann's solution either by mouth or intravenously according to the severity of the case. This is followed by a schedule of feeds of either breast milk or half cream dried milk without added sugar in slowly increasing quantity and strength. Any parenteral infection is controlled by chemotherapy, and blood biochemistry is closely followed and upsets corrected.

TABLE 2
CONTROL CASES

No.	Age (mths.)	Parenteral infection	Intravenous infusion	Chemotherapy	Total days in hospital	Days still stools 4 per day
1	1	—	—	—	21	6
2	2	—	—	—	6	3
3	2	—	—	—	19	9
4	4	—	—	—	26	15
5	2	—	Yes	—	14	3
6	2	Upper respiratory infection ..	Yes	Sulphadiazine	26	10
7	3	,, ..	Yes	,,	19	13
8	6	,, ..	Yes	,,	15	6
9	12	,, ..	Yes	,,	13	3
10	5	,, ..	—	,,	12	3
11	6	,, ..	Yes	,,	21	19
12	6	,, ..	—	—	8	1
13	5	,, ..	—	Sulphadiazine	12	6
14	1	Otitis media ..	Yes	,,	15	5
15	10	,, ..	—	,,	26	2
16	1	Thrush ..	—	—	15	5
17	4	Otitis media ..	—	Sulphadiazine	11	3
18	8	Thrush ..	—	,,	13	1
19	9	Otitis media	—	,,	16	2
20	4	Thrush and Skin infection	—	Penicillin	41	37
21	2	Thrush ..	—	—	13	4
22	3	Respiratory infection .. Phlebitis	Yes	Sulphadiazine and Penicillin	25	20
23	3	Tonsillitis ..	—	Sulphadiazine	13	2
24	3	Otitis media ..	—	,,	11	4
25	8	,, ..	Yes	,,	13	8

In the 'trial' series arobon in water only was given for the first twenty-four hours in place of Hartmann's solution. This was followed by the usual schedule of oral feeds, to which arobon was added. Seriously dehydrated patients were first put on intravenous infusion only for twenty-four hours before the arobon administration was started. Arobon was used in 5 per cent. strength for infants up to six months of age and 10 per cent. strength over six months, and was continued for a varying time according to the response of the patient, the average time for all cases being nine days.

During the six months' period twenty-five cases in each series were treated and an analysis of their main features is given in tables 1 and 2. Two cases in the arobon series are not included; one infant developed pyaemia which needed prolonged treatment, another had to be taken off arobon after one day because of severe vomiting. It will be seen that the two series are roughly comparable: (a) in age group: the average age was 4·5 and 4·3 months respectively and the number of cases under three months of age in each series was eight; (b) in severity: seven and nine cases respectively needed intravenous infusion; (c) in incidence of parenteral infection: four and five cases respectively were primary gastro-enteritis.

Discussion of Results

These cases were in general severe grades of gastro-enteritis with general toxic manifestations and some degree of dehydration. The great majority of the cases had some form of parenteral infection which responded to chemotherapy; only a very few were of the primary type of enteral infection. This is in keeping with our usual experience in this unit.

Two figures are taken in an attempt to find an objective guide to the rapidity of cure: the total length of stay in hospital, and the number of days required to reduce the stools to four or less per day and to show an appreciable improvement in their consistency. The average figures dividing primary cases from those with parenteral infection, are given in table 3.

In the parenteral cases the addition of arobon showed no improvement in results. Recovery depended chiefly on the control of the primary infection.

In the few cases of primary gastro-enteritis it would seem that arobon quickly controlled the number of stools, and also the average length of stay in hospital was slightly reduced. It is difficult to draw conclusions from only four cases, but it was found that when the disease was severe the response in the general condition of the patient to

TABLE 3

AVERAGE FIGURES DIVIDING PRIMARY CASES FROM THOSE WITH PARENTERAL INFECTION

	Average stay in hospital (in days)	Average time before stools reduced to 4 per day (in days)
Arobon cases		
Enteral cases ..	15·2	2
Parenteral cases..	20	8·3
All cases ..	19	7·2
Control cases		
Enteral cases ..	17·2	7·2
Parenteral cases..	16·9	7·7
All cases ..	17	7·5

restorative measures was no quicker in spite of the rapid reduction of stools. It was in the milder degree of disease that the response to arobon was most encouraging.

Our results do not confirm the promising reports of the previous trials, but the high incidence of parenteral infection found in our series may largely account for this. In our experience infantile gastro-enteritis in its severer grades is a generalized disease, and any treatment directed to the alimentary tract alone has not been found to exert any appreciable effect.

Some other results of arobon administration were observed during the trial.

1. Older infants often dislike the taste and are reluctant to take arobon.

2. Arobon tends to aggravate any tendency to vomit. Three patients had to be taken off the treatment on the second, fifth, and sixth days respectively because of severe vomiting.

3. It is stated in the Swiss literature that arobon absorbs all the fluid portion of the stool. In our experience this is not strictly true. It certainly absorbs a large part of the fluid and all the faecal matter and is passed as a brown paste, but some fluid is often passed at the same time. This is colourless and odourless and is immediately absorbed into the napkin, so that its presence can be overlooked if its passage is not actually observed.

4. Addition of arobon does not prevent relapse. Four cases in the arobon series and two cases in the control series had a recrudescence of symptoms after a short period of improvement.

Conclusions

1. In cases of gastro-enteritis with parenteral infection, cure of the disease depends upon control of the primary infection and the addition of arobon exerts no appreciable effect.

2. In primary gastro-enteritis arobon can appreciably reduce the number of stools passed and in such cases may be useful as symptomatic treatment, but it is doubtful whether it speeds recovery in severe cases.

3. Arobon does not prevent relapse.

4. In the presence of severe vomiting it is not always tolerated.

5. It may be that arobon has a more useful place in the treatment of early or mild cases when its symptomatic action would serve more purpose.

Summary

A new therapeutic agent advocated in the treatment of gastro-enteritis is described. A short history of its discovery and of previous reports of its use are given, followed by a description of its trial on cases admitted to a gastro-enteritis unit over a period of six months. The conclusions drawn do not confirm previous reported results, but it is considered that further trials are indicated in primary gastro-enteritis as it might well prove useful in early cases of this type.

I am indebted to Dr. Bernard Schlesinger for his help in preparing this paper and for permission to publish these cases treated under his care, and also to Messrs. Nestlé Ltd. for their generous supply of arobon for the trial.

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EPIDEMIC GASTRO-ENTERITIS OF INFANTS IN ABERDEEN DURING 1947

BY

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Gastro-enteritis in infants continues to attract much attention and numerous papers on this subject are published. The prevalence of this disease and the high mortality often associated with it make it most desirable that further investigations should be undertaken in order, if possible, to determine the etiological cause or causes and to devise methods of prevention and control. It will be sufficient here to mention a few of the more recent contributions to the study of the general epidemiology of the disease such as those by Payling Wright (1946) and Deeny and O'Brien (1946), and to the records of specific outbreaks by Ormiston (1941), Bloch (1941), Brown et al. (1945), Bray (1945), Gunn (1945), Gairdner (1945), and Giles and Sangster (1948).

Infantile Mortality in Aberdeen

Since infantile gastro-enteritis is not a notifiable disease the only basis for comparing the disease incidence during 1947 with that of previous years is provided by the infant mortality rate and the death rate due to diarrhoeal diseases in children under one year. A steady fall in the infant death rate has been apparent in Scotland generally since 1915, and in 1946 Aberdeen's infant mortality compared favourably with that of the rest of Scotland. Thus the infantile mortality rate was 140 in 1915 and 50 in 1946, while the deaths from diarrhoeal diseases dropped during the same period from 57 to 8·5 per 1,000 births; the year 1947, therefore, with its total infant mortality of 64 per 1,000 live births and a corresponding rise in the death rate due to diarrhoea marks a substantial increase which was due almost solely to the epidemic of gastro-enteritis.

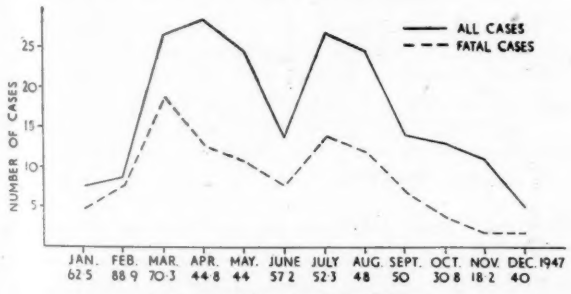

FIG. 1.—Seasonal incidence.

Present Series

Out of a total of 415 infants with diarrhoea who came under observation during the year, 207 were diagnosed as infective gastro-enteritis of uncertain etiology. Of these 207 cases, no less than 105 died, which amounts to an overall case fatality rate of 50·6 per cent., and eighty-three of the fatal cases belonged to the City while twenty-two had originally been transferred from the County to City Institutions. Out of eighty-three infants who were gravely ill at the onset, fifty-eight eventually died, giving a case fatality of 69·9 per cent.; a further 104 infants were moderately ill on admission and forty-seven or 45·2 per cent. died; the remaining twenty cases were mild and all recovered.

Age-Sex Incidence

The maximum incidence was associated with the first trimester with a peak at the second month and, in fact, fully a third of the cases were under two months, and 87 per cent. of the babies affected were within the first seven months of life. After seven months the figures decline sharply and only nine were more than one year old. On the whole the fatality rate appeared to be fairly constant for each monthly age-group in the first year of life. As regards sex, males were affected more frequently than females, although the mortality rate was practically the same in both (table 1).

Seasonal Incidence

The months with the greatest incidence of cases were March and April, with a further sharp rise in July (fig. 1), while the quarterly incidence of the disease was: first quarter forty-four cases, second quarter sixty-seven, third quarter sixty-five, and

TABLE 1
SEX INCIDENCE OF CASES

	Total cases	No. of fatal cases	Case fatality
Males	114	56	49·2
Females	93	49	52·7
	207	105	50·6

fourth quarter twenty-nine. The peak incidence of gastro-enteritis used to occur during the third quarter of the year when the atmospheric and ground temperatures had risen above a certain minimum. In this connexion it is interesting to observe that the two periods with a peak incidence coincided with the coldest March (6·1° F. lower than the mean monthly average) and the hottest July (2·7° F. above the mean monthly average) recorded in Aberdeen during the last fifty years; therefore the incidence of gastro-enteritis does not appear to be confined to the hot seasons. The mortality was highest in February, and the unusually cold spell at that time may have been a contributing factor since chest complications were more common during that month and these always rendered the outlook more precarious. However, it will be seen from fig. 2 that the nosocomial infections outnumbered the external infections in the first four months of the year, and were largely responsible for the first peak in the incidence.

Hospital and Institutional Infection

There can be little doubt of the infective nature of gastro-enteritis, although the original source of infection often remains obscure, and the actual mode of spread can only be conjectured since the causative agent has not been specifically determined. In the present series 122 cases, or 58·9 per cent., were believed to have contracted their infection in hospital wards or institutions. Not infrequently patients were admitted to the various hospitals with a diagnosis of gastro-enteritis when there was no indication of a gastro-intestinal disturbance of any kind or merely a mild diarrhoea which responded to suitable dietetic treatment. After a period of five to ten days in hospital, cases of this type would suddenly develop the clinical signs and symptoms of severe gastro-enteritis.

The first ward outbreak, involving four cases, occurred towards the end of February, and three weeks later another group of eight cases appeared in the same ward, four of them simultaneously. The ward was used for the treatment of respiratory infections in children and babies, and at the time of the second outbreak twelve patients under the age of two years were being treated and thus the disease affected 66·6 per cent. of susceptible subjects, and further, all but one of the affected cases died.

Another outbreak which it was possible to study in some detail took place in another ward of the same hospital. This outbreak involved seven cases, four of which proved fatal. The first case had previously been transferred to the cubicle isolation ward for suspected gastro-enteritis and after a week's observation was transferred back for treatment of his original chest infection. Thirteen days later he developed true gastro-enteritis and died. In the other six cases, the first symptoms appeared within a fortnight of the re-admission of the first case to the ward and three died.

Four other distinct outbreaks were observed, two of these occurred in a second hospital, the third in another, and the fourth in a nursery. Two outbreaks in the medical and surgical wards of a children's hospital involved seventeen cases, fourteen of whom died. An outbreak of neonatal infection affected fourteen infants and nine died, while in the infants' nursery in which children with unsatisfactory home conditions were cared for, eight cases contracted infection and six died.

As a result of the first two outbreaks in hospital No. 1, it was decided to admit all infants with a doubtful history or symptomatology to a cubicle isolation ward set aside for the purpose. This procedure seemed to limit the extent of hospital infection but even in the cubicle ward there appeared to be some evidence of cross infection. It was never possible to establish how the infection was carried from one patient to another, though a breakdown in nursing technique through shortage of staff, particularly at night, seems to be the most probable explanation.

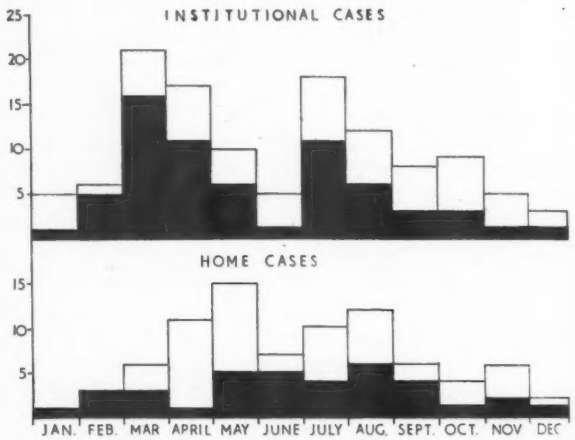

FIG. 2.—Institutional and non-institutional cases: total cases and deaths for each month.

Fig. 2 shows the institutional and hospital infections in parallel with those cases who were thought to have contracted the disease at home. It is obvious that to prevent epidemics of gastro-enteritis in hospitals and institutions for the care of infants the wards must be reconstructed and staffed in such a way as to limit the spread of infection. Cubicle isolation wards with complete sterilizing equipment and a nursing staff sufficient in number to maintain a complete eight-hour shift, and with specified duties, should be the aim in the administration of such hospitals.

Incidence and Distribution of Outside Infections

The highest incidence of cases occurring outside institutions was in April (eleven cases), May (fifteen cases), and August (eleven cases), and the

TABLE 2

COURSE OF GASTRO-ENTERITIS IN 207 CASES

Acutely ill at onset	Death within 72 hours		14
	Steady deterioration and death		17
	Initial improvement and sudden relapses ..	Death	22
		Recovery	14
	Ensuing marasmus	Death	5
		Slow recovery	5
	Uneventful recovery		6
	Total		83
Moderately ill at onset	Steady deterioration and death		16
	Initial improvement and relapse	Death	27
		Slow recovery	27
	Ensuing marasmus	Death	4
		Slow recovery	9
	Uneventful recovery		21
	Total		104
Mild at onset	Relapse and recovery		2
	Uneventful recovery		18
	Total		20

case mortality amongst patients who contracted their infection at home was 44·4 per cent. as compared with 58·9 per cent. in the institutional cases. A higher death rate among hospital infected cases might, however, be expected since the effects of gastro-enteritis were bound to be more severe in those who were suffering from, or had just recovered from another disease. Seventy out of the total of eighty-one home-infected cases came from the City of Aberdeen, and the remaining eleven from other burghs and County districts in the north-east of Scotland. The majority of cases were apparently unrelated, although the series included five sets of twins, and in ten more cases contact with a previously infected case could be established. The seventy City cases, with four exceptions, all came from crowded and mostly slum areas and a temporary hutted encampment in which eleven cases occurred, with nine fatalities.

Predisposing Factors

That artificial feeding is one of the most important predisposing factors in the causation of gastro-enteritis has been known for a long time. In the present series only four infants, or 1·9 per cent., had been entirely breast-fed. In the remaining 203 patients, breast-feeding had been replaced or supplemented by the bottle for at least a week before the onset of symptoms. Another predisposing factor encountered in the present investigation, and already well recognized, was debility from defective nutrition or previous disease; sixty-three cases, or 30·5 per cent., had an infection before contracting gastro-enteritis.

Clinical Findings

There is little point in again giving a detailed account of the clinical findings, as they do not

TABLE 3

RELATION OF ONSET TO DURATION AND END RESULTS OF ILLNESS

Length of illness in weeks	Acute onset			Insidious onset			Combined
	Recovered	Died	Total	Recovered	Died	Total	Total
0–1 ..	2	13	15	3	1	4	19
1–2 ..	19	26	45	12	4	16	61
2–3 ..	25	11	36	3	4	7	43
3–4 ..	12	5	17	3	6	9	26
4–5 ..	9	5	14	2	3	5	19
5–6 ..	3	1	4	–	1	1	5
Over 6 ..	–	1	1	1	–	1	2
			132			43	175

appear to have differed substantially from those which have already been described.

The incubation period has often been very difficult to determine with certainty, both in cases which contracted their infection outside and inside institutions. This is probably due to the fact that it is often very difficult to determine when a particular infant started to develop the disease; also it is impossible at the moment to determine the length of infectivity of a particular case. At best it can at present be concluded that the incubation period of the disease may be as long as thirteen days, is probably never less than two days, and may be commonly two to ten days.

The progress of the course of the illness in the 207 cases which came under observation is given in table 2. Apart from the high number of deaths, 105 out of 207, the other marked feature is the relapse rate. Ninety of the cases showed evidence of relapse, and of these forty-seven died. This occurrence raises the question as to the possibility of more than one type of agent being responsible for the disease, and to the possibility that in the course of nursing these cases a cross infection occurs. On the other hand the relapse may be a normal consequence in the course of the illness.

During the whole year 180 cases came under direct observation in the City Hospital and an analysis of the initial symptoms showed the following incidence:

Onset sudden	132
,, insidious	43
,, uncertain	5
Pyrexia	variable
Vomiting	109
Abnormal stools	43
Vomiting and abnormal stools	28
Anorexia	18
Convulsions	3
Dehydration—mild	128
,, severe	52

The relation of the type of onset to the duration and end result of the illness is given in table 3. From this it will be seen that after the exclusion of five cases in which the type of onset was uncertain, approximately 70 per cent. of cases terminated within three weeks. With regard to more protracted cases, there was occasional difficulty in determining exactly the cessation of the active phase since in many cases the stools were persistently abnormal and weights tended to fluctuate, although appetite was good and fairly normal feeds were tolerated. The average duration of all cases (180) was 17·1 days; for the fatal cases 15·7 days; for survivors 19·5 days. Three cases which might be described as fulminating died within thirty to forty-eight hours of the onset, and one case continued as long as sixty days. The presence of parenteral infection as a contributory cause of the disease has been studied by many workers and considerable controversy has arisen as to whether such an occurrence is part of the disease or simply a complication. In the series of 180 cases which have been under observation in hospital during the year, parenteral chest infections were prominent in thirty-nine cases, and a further eleven showed pulmonary involvement at a later stage. The question of inflammatory changes in the middle ear have been specially studied, but only in eight cases has evidence of middle-ear disease been obtained, and recognizable mastoiditis was not encountered.

Pathological Findings

In all a series of fifty-five autopsies was carried out over the year, an increase of thirty-one as compared to the series already reported (Giles and Sangster, 1948). These additional autopsies did not add materially to the knowledge which had already been obtained, and accordingly only a brief summary of the results need be given. A certain number of cases which died outside the City Hospital have been included in the series.

Respiratory tract. The upper respiratory tract showed no changes of any note. True pneumonic consolidation was found in fourteen out of fifty-five cases, while a further fifteen showed some basal congestion. In most instances the pneumonia or bronchopneumonia appeared to be a terminal event.

Cardiovascular system. In forty-five post-mortem examinations the heart and blood vessels were normal; six cases exhibited pallor of the myocardium although microscopic examination failed to show any significant change; fatty degeneration was observed in one, and myocarditis with small foci of necrosis and round-cell infiltration in another. Two patients had been diagnosed as suffering from congenital heart disease, and at autopsy one was found to have a patent foramen ovale and the other a patent inter-ventricular septum.

Alimentary tract. An infant who has suffered from a profound gastro-intestinal disturbance for days and even weeks might be expected to show well-marked changes in the stomach and intestine. It is, however, remarkable how often the gastro-intestinal tract was devoid of any definite pathological change, either macroscopically or on histological examination. In the cases under discussion the oesophagus was invariably normal. The stomach was dilated in seven cases, all of which had received gastric drips before death. In eleven instances sub-mucous haemorrhages were present, a further nine merely showed congestion and oedema of the mucous membrane, while in thirty-five no abnormality could be found. The post-mortem appearances in the intestine varied, and in the more fulminating cases the appearances were more marked than in those with a more prolonged illness. The small intestine was normal in fourteen cases; on thirteen occasions sub-mucous haemorrhages were encountered with marked mucosal congestion, whereas the remaining twenty-eight exhibited only mild hyperaemia, chiefly of the lower half of the ileum. True ulceration of the intestine

was observed in only four cases. The large bowel was less frequently involved than the ileum, since in twenty-one out of fifty-five necropsies no naked-eye or histological lesions could be detected. A further twenty-four showed mild congestion, while only ten cases were characterized by haemorrhages and ulceration.

Abdominal viscera. The liver was the only organ which consistently showed some evidence of damage. This varied from slight fatty degeneration to generalized fatty changes and necrosis with little healthy liver parenchyma remaining. On eight occasions there was no fatty degeneration but the liver sinusoids were engorged while the remaining forty-six showed some degree of fatty change. In twenty of the latter the fatty degeneration was advanced, involving the whole lobule. Liver damage in itself does little to elucidate the etiology of gastro-enteritis for it is frequently seen in infants who have died from other causes. Nevertheless, it is reasonable to suppose that the degree of liver damage is one of the most important prognostic factors. In view of the peripheral distribution of earlier fatty lesions it seems probable that the cause of these changes might be sought for in portal toxaemia.

The spleen was found to be normal in thirty-six and congested in the remaining nineteen autopsies. The evidence of renal damage, though less spectacular than that of the liver, was nevertheless observed in a large proportion of cases. On seventeen occasions a variable degree of tubular degeneration was present, consisting of cloudy swelling of the convoluted and fatty degeneration of the collecting tubules. Four cases exhibited interstitial infiltration with small round cells and small medullary haemorrhages. Nineteen cases showed passive congestion of the kidney only, and in the remaining fourteen no abnormalities whatsoever were observed.

Lymphatic system and endocrine glands. The mesenteric nodes were often swollen and congested. In twelve specimens examined histologically five showed polymorphonuclear infiltration and oedema, while the remaining seven were congested. In three cases medullary haemorrhages were observed in both suprarenal glands; each of these patients had a sudden collapse just before death as in a true Waterhouse-Friderichsen syndrome. Seven other cases showed well-marked congestion of the adrenals, but histological examination revealed no significant changes. No other abnormalities of the endocrine system were observed.

Central nervous system. In the fifty-five cases which were examined post-mortem three showed abnormalities in the cerebrospinal fluid before death, in the shape of increased protein, 50 to 80 mg. per cent., and increased cells, 13 to 21 lymphocytes per c.mm. In eighteen cases the brain and pia-arachnoid were congested, and in thirteen instances small perivascular haemorrhages were observed macroscopically and on histological examination. Obvious cerebral oedema was noted in three fulminating cases. One case, a male infant aged six months, showed an extensive purulent meningeal exudate most profuse around the base of the brain and along the Sylvian fissure. Culture of the meningeal exudate yielded a pure growth of Bact. coli neapolitanum. Until a short time before death there was no evidence of meningitis, so this complication was probably a terminal one. Despite the reports by Scandinavian workers, histological examination of the brain tissues failed to show any evidence of perivascular round-cell infiltration.

Middle ear and mastoid. Although the middle ear and mastoid were examined in every case, in only five was there evidence of a purulent exudate. In two of these Bact. coli neapolitanum was isolated, while in the remaining three culture yielded a mixed growth of staphylococci, Str. viridans, and a diphtheroid organism.

Bacteriology

Despite a great deal of research work the etiology of the disease has not so far been settled. Certain workers have tried to establish a relationship between such organismal causes as Str. faecalis, a specific virus, and certain types of coliform bacilli and the disease. Gale (1944) for instance described strains of Str. faecalis, belonging to Lancefield Group D which could be obtained from cases of infantile gastro-enteritis. This organism produces tyramine, a substance considered to be toxic to young children, and which caused diarrhoea when injected into rats. As regards the virus theory, Barenberg and others (1936) found in some fatal cases mononuclear lung infiltrations which suggested the possibility of a virus infection. Lembcke and others (1943) identified a filterable agent lethal to mice in the faeces of infected babies. Light and Hodes (1943) claimed to have transmitted the disease to calves by the nasal introduction of faecal filtrates and these results were confirmed by Buddingh and Dodd (1944). The virus theory has had some support from the work of Christen and Biering-Soerensen (1946), who found evidence of encephalitis in the shape of round-cell infiltration. On the other hand Pappenheimer and Enders (1947) demonstrated inclusion bodies in the cells of the intestinal mucosa of cases suffering from enteritis. Various strains of coliform organisms have also been suggested as causal agents from time to time. Thus in 1927 Adam concluded that a special type of Bact. coli, characterized biochemically by the fermentation of saccharose and rhamnose was found regularly in the faeces of infants with gastro-enteritis. Less frequently he isolated a different type of coliform which was related to one of Jensen's calf strains. Adam's observations were later confirmed by Czīglány (1941) during an epidemic in Budapest. In 1945 Bray, in this country, published work on a series of fifty-one cases, in over 90 per cent. of which he recovered a serologically homogenous type of Bact. coli neapolitanum

TABLE 4

THE INCIDENCE OF BACT. COLI TYPE GASTRO-ENTERITIS IN 415 CASES OF INFANTILE DIARRHOEA

Clinical diagnosis	No. of cases positive for type GE	No. of cases negative for type GE	Total No. of cases	Percentage of positive cases
1. Gastro-enteritis:				
(*a*) Fatal cases	99	6	105	94·3
(*b*) Cases which recovered	97	5	102	95·1
(*c*) Total	196	11	207	94·7
2. Diarrhoea attributable to other causes:				
(*a*) Non-infective	1	66	67	1·5
(*b*) Secondary	5	79	84	6
(*c*) Specific infective (dysentery, etc.) ..	0	10	10	0
(*d*) Total	6	155	161	3·7
3. Diarrhoea of doubtful origin	17	30	47	36·2
All cases of diarrhoea	219	196	415	52·8

characterized by a peculiar seminal odour when grown on artificial media. A few of the strains, although serologically identical, failed to ferment lactose and should, therefore, be classified as paracolon bacilli. The serology of the coli groups of organisms has been re-investigated in the light of modern knowledge, and this work has been reviewed by Kauffmann (1947) who has also participated largely in its development. The identification of O, K, and H antigens has led to the establishment of a diagnostic antigenic scheme by means of which the coli strains can be classified in O groups and types. Not all members of the coli groups are in possession of an H antigen, and the K antigens which are associated with the envelope or capsule also play an important part. The Vi antigens include thermolabile antigens (L and B) as well as thermostabile antigens (A), while the L and B antigens are mostly envelope antigens corresponding to the Vi antigen, the A antigens appear mostly as visible capsules. O inagglutinability at 37° C. is also of frequent occurrence and is due to the presence of one of the K antigens, particularly the L. It may be possible, therefore, that the new knowledge of the serology of the coli group will help to elucidate certain problems connected with the pathogenicity of this organism.

During the course of the epidemic the bacteriological investigation was concentrated on the examination of faeces for (1) Group D streptococci, (2) a possible virus, and (3) special types of Bact. coli. After a considerable amount of work the examination of specimens for Group D streptococci was stopped as this part of the investigation did not seem to be leading to any conclusive result. Similarly after a series of faecal specimens had been filtered and the filtrates injected into the allantoic membranes of developing chick embryos no evidence of the transmission of a virus could be obtained. Work was, therefore, concentrated largely on special types of B. coli.

Preliminary work on the serology of the coliform organisms showed that one particular type was frequently present, and through the kindness of Dr. R. D. Stuart of Glasgow, cultures and antisera of the organism isolated by Bray were compared with those isolated here, when the various strains were found to be identical. The methods used in the isolation and identification of the organism, the cultural characteristics, and its antigenic properties have already been described (Giles and Sangster, 1948) and it will only be necessary here to give the results of the investigation over the whole year.

A total of 2,150 specimens of faeces from cases and controls were examined between Jan. 1 and Dec. 31, 1947. The results of these tests in 415 cases of infantile diarrhoea are summarized in table 4. This shows that the B. coli neapolitanum type of organism was present in 94·7 per cent. of cases as opposed to 3·7 per cent. in cases of diarrhoea attributable to other causes. That the presence of this type of organism could not be due simply to cross infection in the wards of the various hospitals was proved by the fact that cases contracting their infection while within their homes showed it as frequently as those contracting their infection in the various institutions. Further, since the first specimens were taken as soon as possible after the patient was admitted there was little chance of their presence being due to cross infection at this stage.

The association of the organism with the disease was, however, even more consistent; thus the faeces of eighty-four out of the total of ninety-seven positive cases which recovered were repeatedly examined at four- to five-day intervals throughout the course of the disease, and in seventy-four cases the organism disappeared from the stools when

clinical improvement occurred, while in the remaining twelve Bact. coli type neapolitanum was still present when the patients were discharged from hospital. Five of the latter were negative on re-examination as out-patients a month later, and the rest did not return for examination. As a rule the disappearance of this type of Bact. coli coincided fairly closely with clinical improvement, but the patients who passed into a state of marasmus proved exceptions. The onset of marasmus was always insidious, and with these cases, although the organism disappeared from the stool the patient's condition remained precarious. Bacteriological specimens taken at forty autopsies showed the presence of the gastro-enteritis type of Bact. coli in the stomach and in the small and large intestines in thirty-five. In five cases which had developed marasmus the organism had disappeared. In ten necropsies the gastro-enteritis type was recovered from the liver, the spleen, the mesenteric glands, and on two occasions from the purulent exudate in the middle ear, and in one instance from the meninges.

In infants suffering from what appeared clinically to be non-infective diarrhoea (dietetic and metabolic disturbances) the organism was isolated from 1·5 per cent. of cases, while in those cases suffering from what appeared to be parenteral infections the incidence was higher, namely 6 per cent. That the organism was also recovered from a substantial proportion (36·2 per cent.) of cases in the group of diarrhoea of doubtful etiology is not surprising, for this group probably included some cases of gastro-enteritis not definitely diagnosed as such owing to complicating parenteral infection or lack of clinical data.

In order to assess the significance of the association between Bact. coli type neapolitanum and cases of gastro-enteritis, specimens from an extensive series of 271 infants under the age of two years without diarrhoea, and a group of 450 adults and older children with or without diarrhoea were examined for the presence of the organism. As seen in table 5, Bact. coli type gastro-enteritis was not found in any of the forty healthy breast-fed and only in seven of the 231 bottle-fed infants without diarrhoea, six of these seven control cases being ward contacts of cases of gastro-enteritis. A small number of adults and older children (six in all) showed the presence of the organism in the faeces, one of these being a nurse in one of the wards where an outbreak of the disease had occurred, and another being a patient suffering from mucous colitis. From the above it is clear that the organism under discussion was associated throughout the year very closely with cases of gastro-enteritis, and not with other conditions.

In order to ascertain whether the presence of this coliform produced an antibody-response in patients from whom it was recovered, the sera of forty-one cases were examined for agglutinins to the organism in question. In twenty-one out of the forty-one cases an antibody-titre of from 1 in 40 to 1 in 640 was observed, whereas no significant agglutination occurred with the sera of fifty-three normal infants and in only three out of 127 sera chosen at random from routine specimens. ' O '-suspensions of the organism were, on the whole, more readily agglutinable than living bacterial suspensions.

Attempts to produce gastro-intestinal infections in young animals by means of feeding them on that particular type of Bact. coli were only partially successful. Young mice, rabbits, guinea-pigs, and kittens were used. The only positive results were obtained when three litters of altogether ten newly born guinea-pigs were fed on the organism. Five out of these ten developed diarrhoea, and three subsequently died within forty-eight hours. Bact. neapolitanum was isolated at autopsy from the blood stream, intestine, liver, spleen, and meninges in all three animals, which also showed fatty changes in the liver and the renal tubules and congestion of the intestinal mucosa and the meninges comparable to those encountered in the human.

However, in the month of November it was noticed that Bact. coli neapolitanum was less frequently associated with cases of gastro-enteritis than had previously been found. Other coliform organisms were obtained from definite cases and anti-sera were prepared for their ' O ' and ' K ' antigens. By this means another fairly frequently occurring type was identified and has been named for convenience the ' Beta ' variety.

TABLE 5

THE INCIDENCE OF BACT. COLI TYPE GASTRO-ENTERITIS IN A GROUP OF 721 CONTROLS.

	No. of cases positive for Type GE	No. of cases negative for Type GE	Total No. of cases	Percentage of positive Cases
1. Breast-fed Infants without diarrhoea ..	0	40	40	0
2. Bottle-fed infants without diarrhoea ..	7	224	231	3
3. Adults and older children with or without diarrhoea	6	444	450	1·3
All controls	13	708	721	1·8

Up until the end of 1947 the beta type has been found in twenty-one out of forty-eight cases of infantile diarrhoea of all types and in three out of fifty-three healthy infants, and in one out of seventy-four adult controls. The forty-eight cases of infantile diarrhoea which were tested for the presence of the organism included nineteen cases of undoubted gastro-enteritis. That the organism has some epidemiological significance can be shown by the fact that two babies from one house were admitted to different hospitals and both showed this Beta type of organism.

The cultural appearance of this organism is in no way different from other coliforms. It is, however, definitely motile, and therefore presumably must have an 'H' antigen. It ferments lactose, glucose, mannite, saccharose, and dulcitol with the production of acid and gas, but only produces a slight amount of acid and gas in maltose, and does not ferment salicin. Although the organism is definitely motile it has not been found possible so far to produce a 'H' antiserum, but 'K' and 'O' antisera have been obtained from immunized rabbits without difficulty. So far little cross agglutination has been noted between Bact. coli neapolitanum and the Beta type antiserum, and in fact the antiserum prepared from the organism is as specific as the antisera prepared from strains of Bact. coli neapolitanum. Indeed, almost invariably absorption tests have confirmed the results obtained with the slide agglutination tests.

What the exact significance of the presence of these special types of coliform organisms in the faeces has yet to be determined. The most striking fact is that in the case of Bact. coli neapolitanum the organism has been for the most part recovered only from the faeces of infants with diarrhoea presumably resulting from infective gastro-enteritis, and a similar situation is arising in connexion with the Beta strain. Several questions, therefore, arise: (1) Have these organisms any pathogenic significance? (2) Is their presence in many cases an indication of cross infection? (3) Is it a question of the conditions within the intestine being made suitable for the development and proliferation of these special types of Bact. coli?

It has been noted repeatedly that the faeces from a case may show negative results for these special types of Bact. coli in the early stage of the disease but later on become positive. Whether this finding is simply a normal occurrence or whether it is due to a cross infection it has not been possible to determine. It has been further noted in hospital that a case may show one type of organism to start with and may then apparently show signs of recovering, and later on a recurrence of the disease may show the second type of organism. It is obvious, however, that much more data will require to be obtained to define the exact relationship of these organisms to the disease and to various epidemiological problems associated with it.

Summary

1. An outbreak of gastro-enteritis lasting for the greater part of the year 1947 is described.

2. Out of a total of 415 infants who came under observation, 207 were diagnosed as infective gastro-enteritis, and of these 105, or 50·6 per cent., died.

3. The children most affected were bottle-fed babies under seven months, and the peaks of the epidemic occurred in April and July.

4. Institutional outbreaks were a marked feature of the epidemic, and the occurrence of six definite ward outbreaks is recorded. The incidence of these nosocomial cases emphasizes the infective nature of the disease.

5. The clinical findings have been summarized and have not been found to differ to any extent from those which have been described in other epidemics.

6. Post-mortem examination of fifty-five fatal cases showed once again the indefinite pathology associated with this disease. The changes that occurred in the intestines were often minimal, but more frequently the liver was affected to a greater or lesser extent, and the damage varied from slight fatty degeneration to generalized fatty changes and necrosis with little healthy liver parenchyma remaining. There were manifestations of toxic action on the kidneys but no evidence of a virus infection in the central nervous system.

7. Attempts to demonstrate a virus were unsuccessful and no association between Group D streptococci and the disease could be established. Examination of the coliform flora showed that Bact. coli neapolitanum could be recovered from 94·7 per cent. of cases of gastro-enteritis as against an incidence of 3·7 per cent. of cases of diarrhoea attributable to other causes. In infants suffering from what appeared to be dietetic and metabolic disturbances the organism was isolated from 1·5 per cent. of cases, while in diarrhoea associated with parenteral infections the incidence was slightly higher, namely 6 per cent.

8. In November, 1947, a second type of coliform organism (the Beta variety) became more frequently associated with the cases. It was recovered from twenty-one out of forty-eight cases of infantile diarrhoea, from three out of fifty-three healthy infants, and one out of seventy-four adult control cases. In the faeces of forty breast-fed babies it was not found at all, in 231 bottle-fed infants without diarrhoea it was found seven times, and in specimens from 450 older children and adults it was recovered only six times.

9. The relation of these coliform organisms to the disease has been discussed but no definite conclusion has been vouchsafed.

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ROSEOLA INFANTUM

AN OUTBREAK IN A MATERNITY HOSPITAL

BY

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Roseola infantum was first described by Zahorsky (1910), and since this time cases have been recorded by many writers both in America and Europe but the disease has received little recognition in England. It has been labelled exanthem subitum and sixth disease but Zahorsky (1947) and others have put forward a plea for the retention of the name roseola infantum or the ' rose rash of infancy '.

The infectious nature of the disease was discussed by Barenberg and Greenspan (1939), who report it to be periodically epidemic in an institution for children and describe an epidemic of twenty-seven cases occurring over a period of three months, the incidence of infection in the respective wards being 35 per cent. and 45 per cent. The incubation period was five to fifteen days with an average of twelve days. Cushing (1927) describes an epidemic in Montreal with incubation periods between eight and fourteen days.

Most cases occur during the first two years of life, and the maximum incidence seems to be between six and eighteen months of age. Conte et al. (1944) found 95 per cent. of cases to be under two years of age, and in the series described by Barenberg and Greenspan (1939) 93 per cent. were under this age, the youngest being four months. Dickey (1945) has seen one case at six weeks old, another at nine weeks, and his oldest patient was a boy of four years. Zahorsky (1910) and Greenthal (1941) both cite cases aged eighteen years, and Cutts (1938) records a case aged thirty-one years which he regarded as undoubtedly one of roseola infantum.

Roseola infantum is characterized by an abrupt onset with a rise of temperature up to 103 or 104° F., which persists for two to five days and falls by crisis. A rash appears usually as the temperature falls but may be delayed for a few days. It is macular, rose pink in colour, and spreads from the trunk to the limbs and face, but is most profuse over the trunk; it reaches its maximum in twenty-four hours and fades during the next twenty-four hours, usually without desquamation.

The child may be fretful and irritable as the temperature rises, there may be convulsions at the onset, but generally there is remarkably little constitutional disturbance. Conte et al. (1944) describe eighteen cases occurring in hospital over a ten-month period, and among these nine had one to six convulsions at the onset. Most other writers record fits much less often.

Glandular enlargement is described but does not seem to be a constant finding, although Jennings (1940) stated that enlargement of the posterior cervical glands, without apparent cause in the scalp, in an infant with a high temperature and with no other clinical findings should suggest the diagnosis of roseola infantum, and in fact this sign led him to diagnose 80 per cent. of his cases of this disease prior to the eruption.

Examination of the blood on the second or subsequent days may reveal leucopenia. In the cases described by Barenberg and Greenspan (1939) 50 per cent. showed leucopenia on the third day, 64 per cent. on the fourth day, and only 25 per cent. on the seventh day. A relative lymphocytosis was present in 66 per cent. on the third day and in all the cases on the fourth day. Zahorsky (1947) and others stress that the lymphocytosis is only relative and that the important factor is the decrease in the polymorphonuclear cells.

The mortality rate is nil, and the recovery is rapid and complete.

The etiology has been discussed by Conte et al. (1944), who put forward three possibilities: (1) allergy, (2) grippe-like infection, (3) virus infection. Most writers incriminate the virus although Breese (1941) tried and failed to demonstrate a filterable virus in throat swabs from three of his cases.

An Epidemic in a Maternity Hospital

The following description of an epidemic in a maternity hospital of a disease conforming to descriptions of roseola infantum is thought to be of interest because such cases have not been recorded in England or in such young infants, and also because a proportion of the nurses, mothers, and fathers were also affected.

The outbreak occurred between June 26 and

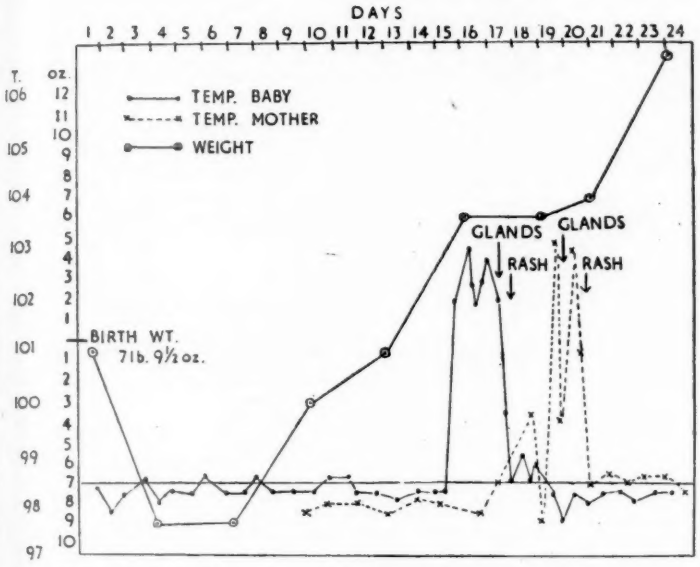

FIG. 1.—Case 7 and mother, temperature and weight.

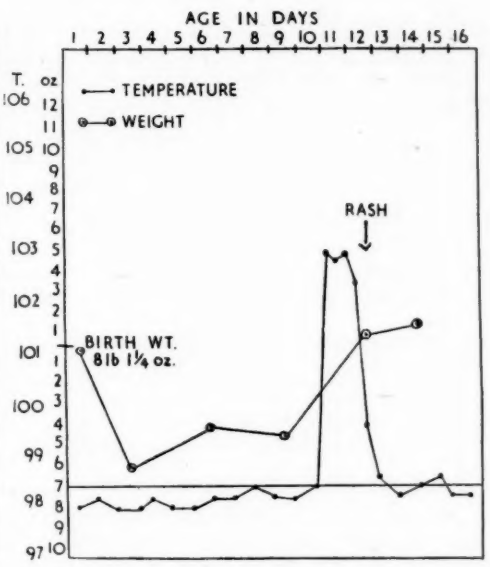

FIG. 2.—Case 15, temperature and weight.

Aug. 7, 1948. During this period there were 144 babies in the hospital, but the epidemic was confined to one floor of the hospital only, on which there were sixty-five babies. Nineteen were thought to have roseola infantum, but in only sixteen was the diagnosis definitely established by clinical findings and by the typical temperature chart. In eight cases (six infants and two mothers) the diagnosis was confirmed by the blood picture. The first two cases were at first labelled as 'pyrexia of unknown origin', and not until we had studied the disease more closely did we include them in the series. The infectivity rate among the babies on the affected floor was 29·2 per cent.

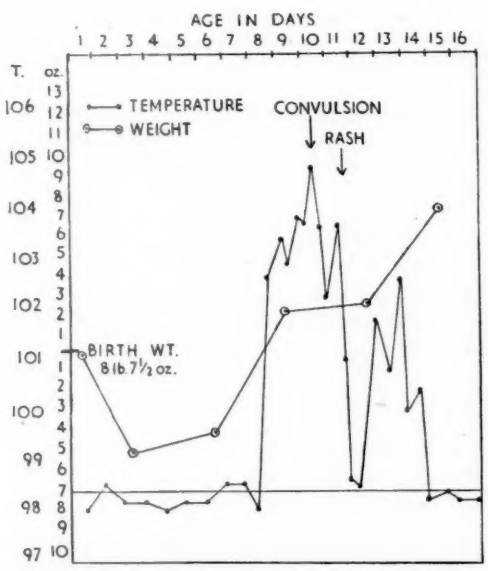

FIG. 3.—Case 17, temperature and weight.

New cases occurred at intervals of one to thirteen days (average two to three days), and the age of onset was eight to twelve days (average eleven days). In one doubtful case the pyrexia started on the fifth day of life, and another baby was eighteen days old when the illness started.

In addition five nurses working on the affected floor developed characteristic symptoms, and a history of a similar illness was obtained from six mothers and four fathers. Three mothers developed the disease while in hospital.

All nineteen babies with roseola infantum were breast fed. A past history of having had rubella was obtained from three of their mothers, one of whom developed symptoms and exanthem of roseola infantum herself while in hospital. Of the remaining mothers, only three were able to say with certainty that they had not had rubella, and thirteen gave a history of measles and one of glandular fever.

Clinical manifestations. The condition was characterized by high fever, rash, and glandular enlargement, and in the majority of cases by an astonishing absence of any constitutional upset. In the adults the clinical picture was rather different and will be dealt with later.

TEMPERATURE. The temperature was an outstanding feature and indicated the onset of the disease. There was a sharp rise to 103° F. or higher (figs. 1, 2, 3); it remained up for twenty-four to seventy-two hours, showing an occasional drop of 0·5 to 2°, but rose again before the characteristic fall by crisis. The temperature then remained normal except in ten cases, where there was a

TABLE

ANALYSIS OF NINETEEN CASES.

Case No.	Age (in days) at onset	Temperature		Rash	Glands	Blood picture							Urine	Comments
		Max. Rise °F.	Fall			Day	Total W.B.C.	% Polys. neut.	% Lympho-cytes	% Mono-cytes	% Eosino-phils	% Path. lymphos.		
1	5	103⁴	Crisis											Lethargy. Physical signs in chest. Mother developed roseola infantum in hospital.
2	8	102	Crisis										Pus ++ B. coli.	Mother and father developed similar disease
3	9	103⁴	Crisis	At onset of pyrexia	Cervical axillary occipital inguinal									Mother and father developed similar disease
4	10	103⁴	Lysis		Occipital axillary cervical								Pus + B. coli. + Strep. faecalis.	Mother developed roseola infantum
5	11	103⁴	Lysis	With fall of temperature	Occipital axillary cervical								Pus + No growth	
6	16	103⁴	Lysis		Occipital axillary								Pus + B. coli.	
7	15	103	Crisis	After fall of temperature	Occipital axillary inguinal									Mother developed roseola infantum. W.B.C. 5,400. Eosino. 1%. Polys. 57%. Path. lymphos. 35%. Lymphos. 4%. Monos. 3%. Paul Bunnell neg.
8	11	104	Crisis	With fall of temperature	Cervical occipital axillary									Lethargy. Transient signs in chest. Broncho-pneumonia.
9	10	102⁶	Crisis	With fall of temperature	Occipital axillary									Mother and father developed similar disease
10	9	102⁶	Crisis	With fall of temperature	Occipital cervical axillary									Mother developed roseola infantum in hospital. W.B.C. 6,200. Polys. 67%. Mono. 7%. Lymph. 24%. Path. lymph. 3%.
11	8	103⁴	Crisis	Prior to pyrexia. Faded with crisis	Occipital axillary	2nd	4,000	29	58	9	1	3		
12	8	103	Lysis	With fall of temperature	Axillary inguinal									Lethargy with pyrexia. Mother and father developed similar disease.
13	11	102	Lysis	At onset of temperature	Occipital axillary cervical	2nd 5th	10,000 10,000	40 65	41 28	10 6	7 6	2 1		Mother developed roseola infantum.
14	11	99⁸	Crisis	At onset of temperature	Occipital cervical axillary	2nd	13,000	43	41	8	—	2		
15	11	103	Crisis	With fall of temperature		2nd 5th	8,200 10,300	18 43	79 54	4 —	4 —	1 3		
16	16	103	Crisis	With fall of temperature	Occipital inguinal									
17	8	104⁸	Crisis	With fall of temperature		2nd	20,000	62	34	17	3	1		Blood count taken after convulsion.
18	18	103	Crisis	With fall of temperature	Occipital axillary	2nd	11,000	80	18	2	—	—		
19	9	103	Crisis	With fall of temperature	Occipital axillary inguinal									Transient signs in chest.

second peak up to 100° F. about forty-eight hours later which was only sustained for a few hours. In one case the temperature rose to only 99·8° F., but the presence of a typical rash, glandular enlargement, and neutropenia made us include this case.

RASH. The rash was seen in fifteen cases. The other four were early cases and it is possible that the rash was overlooked. As can be seen in the accompanying table, the rash usually appeared as the temperature fell or shortly after. In two cases the rash appeared with the pyrexia, and in one it occurred before the pyrexia, but in this case the etiology of the rash is in doubt since it also persisted for eight days.

The rash began on the chest and very soon spread to the limbs, abdomen, and back. In only a few cases was the face involved, and in no cases were the palms and soles affected. The exanthem consisted of macules, 2 to 4 mm. in diameter, which were usually surrounded by an area of erythema. On the back and the limbs the macules tended to be more confluent and in some areas had a scarlatiniform or a morbilliform appearance. All these features were present in different areas in one case at the same time. A macular rash, however, was most usual, and there were never any vesicles or pustules. The rash varied in intensity in the same infant, and usually faded, without desquamation or staining of the skin, in about twelve to twenty-four hours.

ENLARGEMENT OF THE LYMPH GLANDS. This was another prominent feature and was usually noticed soon after the onset of pyrexia. The occipital glands were enlarged in fourteen cases, the axillary glands in fourteen, those of the posterior triangle of the neck in seven, and the inguinal glands in five. In the first two cases of the series enlarged glands were not looked for, whilst in two others the glands were not enlarged, but in these cases other characteristic features were present and therefore they were included in the series.

The glands were enlarged to the size of a pea, were discrete, and never suppurated.

In no case was the spleen found to be enlarged.

OTHER FEATURES. Certain other features were found in some cases. At the onset of the illness in five cases there was some dullness on percussion of the chest, and in two of these moist sounds were audible on auscultation suggesting a bronchopneumonia. These signs, however, disappeared in twelve to twenty-four hours. In some cases there was slight injection of the palate and pharynx, and in some the tympanic membranes were injected, but this was attributed to the pyrexia.

There was no vomiting or diarrhoea, and no jaundice. Most of the babies had normal vigour and fed well. Only four babies lost weight, the maximum loss being 4 oz.; four babies failed to gain weight during the period of pyrexia, and the remainder gained weight steadily throughout.

One infant had a major convulsion at the onset of the infection.

Pathological investigations

URINE. In the early days of the outbreak every case had an examination of the urine performed. Altogether ten specimens were examined and the results are put forward in the accompanying table.

BLOOD. In a number of cases white-cell and differential counts were done on the second or third day of the illness, and in two cases they were repeated several days later. In addition blood counts were done on two mothers who developed the disease while in hospital, and in one of these a Paul Bunnell test was also taken and found to be negative.

Leucopenia and neutropenia were usually found, although in one infant the cell count totalled 20,000 per c.mm. of blood with 62 per cent. of polymorphonuclear cells. This count, however, was taken shortly after a convulsion (see table).

Treatment. No treatment was required in most cases. Those infants with abnormal physical signs in the chest or excessive pus cells in the urine were given penicillin and/or sulphonamides, but no difference was noted in the course of the disease, nor was there any alteration in the temperature curves.

Manifestations of roseola infantum in adults. Five nurses, all of them contacts with the affected babies, developed the disease.

The first nurse developed pyrexia, severe retro-orbital headache, photophobia, and general malaise. There was definite neck rigidity and a doubtful positive Kernig's sign was elicited. She was transferred to an isolation hospital where a lumbar puncture was performed and normal cerebrospinal fluid was obtained. Several days later her temperature fell and she developed a rash. She was discharged without a definite diagnosis having been made.

Four other nurses developed similar symptoms with pyrexia followed by a macular rash, and three of them were transferred to fever hospitals. They were discharged with the tentative diagnosis of atypical rubella.

Three mothers developed a similar condition while in hospital, and we heard from six others who developed severe malaise followed by a rash on the face and limbs after they reached home. The onset was within fourteen days of the onset of roseola infantum in their babies. A similar condition, with very severe retro-orbital headache, has been reported in four fathers. These cases were seen by their private doctors who were unable to make a certain diagnosis but suggested rubella as a possible cause. The mothers themselves felt certain that it was the same disease which they had seen in the babies in the hospital.

The striking coincidence and similarity of symptoms and signs in the nurses and parents led us to conclude that there was a common etiology and that the disease was indeed roseola infantum.

The blood pictures obtained in two mothers was characteristic.

Differential diagnosis. Measles can be excluded by the absence of typical prodromal coryza, the time relationship of the rash to the temperature, and by the differential white cell count. Dickey (1945) gives excellent charts comparing the prodromal periods, the degree and duration of temperature, the fall by crisis or lysis, and the relation of fever to rash in roseola infantum, rubella, measles, and scarlet fever. He also gives charts showing the varieties of temperature curves and the times of appearance of the rash in roseola infantum. The age incidence in our epidemic was also strong evidence against measles.

Rubella was considered a likely diagnosis early on in the epidemic mainly because the first nurse to be affected was provisionally labelled as a case of rubella, but later this was thought not to be so, and she was discharged from an isolation hospital with no definite diagnosis.

The babies developed the disease from the sixth to the eighteenth (average eleventh day of life) and usually the rash appeared after the temperature had fallen by crisis. These two factors together with the blood findings do not suggest rubella. Hynes (1940) performed serial blood counts on sixty-one adults with rubella and concluded that there was a leucopenia at the onset with an absolute lymphopenia, but that an absolute lymphocytosis occurred after the fifth day, the total count rising to normal by the tenth day. He found Turck cells present in every case and plasma cells appeared in from half to two-thirds of the cases. Rosenblum (1945) gives figures for the blood changes in roseola infantum, and shows clearly that there is leucopenia with marked neutropenia by the third day and that the lymphocytosis so often described is only relative.

A high percentage of our cases had generalized glandular enlargement, but glandular fever was excluded by the blood counts, and by a Paul Bunnell reaction in one case.

The clinical picture in the adults differed somewhat from that in the infants but the temperature curves and the time of onset of the rash was similar in all cases. Wallfield (1934) describes a girl of twelve years who was admitted with the clinical picture of encephalitis, but was eventually proved to have roseola infantum. She had a two-day history of high fever, vomiting, headache, vertigo, and stiffness of the neck. The temperature fell by crisis on the third day and a typical rash developed. Her cerebrospinal fluid was normal but her blood count showed the typical changes. There were no sequelae. This description closely resembles that found in our adult cases.

The epidemic described in this paper was, therefore, considered to be one of roseola infantum, but was unusual in that it affected the newborn, and also a relatively high proportion of adults.

Summary

1. A review of the literature concerning roseola infantum is given, together with a description of the disease drawn from these records.

2. An epidemic of roseola infantum occurring in a maternity hospital is described.

3. The differential diagnosis is discussed.

We wish to thank Dr. Van de Merwe for the haematological investigations.

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CASE REPORTS

AN UNUSUAL CASE OF ACUTE LEUKAEMIA

BY

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During the five-year period 1942-6 twelve children suffering from acute leukaemia were admitted to Alder Hey Children's Hospital, Liverpool. They were classified as follows:

Lymphatic leukaemia	7	cases
Monocytic ,,	2	,,
Myelocytic ,,	3	,,

Eleven were boys, and one girl; three of these children were under the age of four years and nine were over four. Ramsay (1927) in a much larger survey (one hundred cases) found that roughly twice as many occurred during the first four years of life as during the subsequent four years and the incidence steadily declines in adolescence. The condition is commoner in males (63 per cent.). The average duration of life is two to four months (Ramsay, 1927; Court and Edwards, 1939). Acute lymphatic leukaemia accounts for 75 per cent. of the cases described by Ramsay; in a smaller series of the same condition reported by Falkenstein and Fowler half the number were aleukaemic. Monocytic and myeloblastic types are much less common.

The case of acute leukaemia now recorded presented several unusual clinical features and a special problem of diagnosis.

Case History

J.H., a boy aged 2 years 9 months, was admitted to Alder Hey Children's Hospital on Oct. 25, 1947, with a three weeks' history of pallor and listlessness. There had been swelling of the left cervical glands for one week preceding admission. He had not lost weight and his appetite was good. His birth and subsequent progress had been normal; he had had no serious illness.

Family history. He was the fifth child of healthy parents. All the siblings living were healthy. The first baby died as a result of birth injury.

Clinical examination. On admission the child was extremely pale but otherwise well-nourished, weighing 30 lb. The temperature was 101° F., the pulse rate 120 per minute, and the respirations 24 per minute. There was bilateral enlargement of the posterior and anterior cervical, axillary, and inguinal glands. The liver edge was one inch below the right costal margin, and the tip of the spleen was just palpable. No abnormal physical signs were found in the nasopharynx, ears, eyes, lungs, heart, or central nervous system.

A blood count made shortly after admission was as follows: haemoglobin less than 28 per cent. (3·6 g. per cent.); red blood cells 1,040,000 per c.mm. of blood; white blood cells 19,900 per c.mm., of which the majority appeared to be blast cells. Platelets were greatly reduced in number. A transfusion of one pint of compatible blood was given on the evening of admission.

Course. Two days after admission a few petechiae were found on the trunk, and small areas of bruising appeared behind the left ear and around the right orbit. This latter area increased in size during the following week with the gradual onset of proptosis and right ophthalmoplegia. An ophthalmological report stated that there was conjunctival oedema, corneal infiltration, and proptosis of the right eye equivalent to 10 mm., but no movement. The optic fundus could not be seen.

Following the blood transfusion the haemoglobin increased to 34 per cent. (4·7 g. per cent.); the red blood cells numbered 1,810,000 per c.mm. and the white blood cells 3,600 per c.mm. of blood. On Nov. 7, 1947, however, the haemoglobin had again fallen to 26 per cent. (3·6 g. per cent.). On this date sternal puncture showed a very cellular marrow with the following differential count: myeloblasts 4·4 per cent.; premyelocytes 1·6 per cent.; myelocytes 28·0 per cent.; metamyelocytes 7·2 per cent.; polymorphonuclears 2·8 per cent.; normoblasts 17·6 per cent.; lymphocytes 4·4 per cent.; smear cells 1·6 per cent. The remaining 32·4 per cent. were cells 7 to 10μ in diameter, with scanty dark blue cytoplasm devoid of granules, and an oval or round nucleus, sometimes indented with rather coarse chromatin threads and up to three indistinct nucleoli. These were finally considered to be atypical myeloblasts.

Proptosis steadily increased and there was much distress, probably due to pain. Early on the morning of Nov. 8, 1947, the night nurse was alarmed to find that the right eye had been extruded and was lying on the pillow. The eyelids were inflamed and oedematous and there was a little purulent discharge from the socket. These local conditions responded rapidly to a course of systemic penicillin (500,000 units daily in six divided doses; total amount given: 5,000,000 units).

Immediately after the loss of the eye the child's general condition improved considerably. The temperature, which previously had ranged between 99° and 100° F., now settled and remained at 98° F., until the terminal phase of the illness. The cervical glands became much smaller and the axillary and inguinal glands and spleen were no longer palpable. The child was happy and contented, interested in his toys and talkative. He remained well for three weeks and gained 1 lb. in weight.

The following investigations were made during this period: the Mantoux reactions, blood Wassermann reaction, and Widal reaction were all negative. Blood urea was 24 mg. per 100 c.cm. Skull and chest radiographs were normal, and urine analysis was also normal (no Bence-Jones protein). Total white blood counts from Nov. 7 to Nov. 27 varied between 2,900 and 8,000 per c.cm. of blood with 40 to 50 per cent. polymorphonuclears, a similar number of lymphocytes, and only scanty immature myeloid cells.

Two further blood transfusions (half a pint on each occasion) were given on Nov. 8 and 13, and by Dec. 4 the haemoglobin was 92 per cent. (12·9 g. per cent.).

Despite the child's general well-being, however, his parotid and submaxillary salivary glands began to increase in size. The mouth and nasopharynx appeared healthy, but haemolytic streptococci (group A) were grown from a throat swab. A further course of systemic penicillin was given (500,000 units daily: total 9,000,000 units).

During the first fortnight in December the haemoglobin level remained fairly constant, but the white cell picture gradually changed, and a count made on Dec. 17 gave 76 per cent. blast cells in a total of 16,700 white cells per c.mm. of blood. Scanty nucleated red blood cells were also present. Sternal puncture on Dec. 9 showed greatly increased cellularity with approximately 95 per cent. blast cells. The peroxidase reaction, morphology, and cell distribution in marrow and peripheral blood indicated that the leukaemia was of myeloblastic type.

During the last two weeks of December his condition began to deteriorate rapidly. Parotid, submaxillary, and cervical glands increased in size and the spleen was felt three inches below the left costal margin. The white cell count rose to 50,000 per c.mm. of blood on Dec. 29, and the cells were practically all myeloblasts. A supply of nitrogen mustard was obtained and treatment started (dose: 0·1 mg. per kg. body weight per day for three days) but the child died on Jan. 1, 1948.

Post-mortem examination. Unfortunately, permission was given for only a limited examination (excluding the brain).

GLANDS. Submaxillary, cervical, and tonsillar glands were enlarged and hard. There was no structural destruction. The thyroid was normal.

CHEST. Heart and lungs appeared normal.

ABDOMEN. The pancreas was enlarged and hard. The kidneys were enlarged and pale, with numerous capsular and subcapsular haemorrhages. The right kidney weighed 256 g. (normal 48 g.); the left weighed 251 g. (normal 49 g.). The spleen was enlarged and hard, weighing 100 g. (normal 37 g.). The liver and alimentary tract appeared normal.

HISTOLOGICAL REPORT. Throughout the kidney, pancreas, and submaxillary glands there was a heavy infiltration of small cells with little cytoplasm and a deeply-stained round, oval, or indented nucleus. Occasional myelocytes and polymorphonuclears were present. In the liver a similar infiltration was largely confined to the periportal areas. In the lymph nodes, and to a lesser degree in the spleen, there was replacement of the normal follicular structure by a uniform infiltration of these cells. The appearances supported the diagnosis of acute leukaemia.

RIGHT EYE. There was complete necrosis of all structures, which included the ciliary body, iris, and parts of the sclera and cornea. There was no evidence of gross inflammatory reaction or tumour.

Discussion

An unusual feature of this case was the loss of an eye. Proptosis occurred as a presenting symptom in three other cases admitted to this hospital, but in none was the process so rapid and extensive that the eye was actually cast off. In the present case the eye appeared normal on admission and the total length of time from the onset of the peri-orbital ecchymosis to extrusion of the eye was twelve days.

Proptosis due to leukaemic infiltration has been reported by Leber (1869) and Werner (1905). Lagrange (1904) collected twenty-five cases and pointed out that the symmetrical nature is a fundamental characteristic. In the case recorded no infiltration of the left orbit was observed. The corneal oedema and infiltration precluded examination of the right fundus. This feature is unusual, but could be accounted for by raised intra-ocular tension due to orbital venous congestion. No case can be found in the literature of spontaneous expulsion of an eyeball due to leukaemic proptosis.

A provisional diagnosis of acute leukaemia was made on admission but was later reconsidered in view of the apparent initial response to treatment, with remission of symptoms and normal blood picture four weeks after admission. Alternative diagnoses were then suggested. Septicaemia or toxaemia were first considered in view of the fact that either condition could depress bone marrow activity and produce a leukaemoid blood picture. The apparent response to penicillin and blood transfusion lent further support to this possibility. Consideration was also given to the possibility of suprarenal neuroblastoma, with secondary deposits in the eye and bones; chloroma; Hand-Schüller-Christian disease; or multiple myelomatosis, all of which might inhibit haemopoietic function. A diagnosis of acute infective mononucleosis, as a

cause of generalized lymphadenopathy and splenic enlargement, was considered unlikely as the mononuclear cells were mainly primitive cells and did not resemble the abnormal type usually found in this condition. The enlargement of parotid and submaxillary glands raised the question of sarcoidosis or Mikulicz syndrome. Syphilis was excluded on the negative Wassermann reaction. Finally, lymphosarcoma could not be disproved until histological sections confirmed the original diagnosis of acute leukaemia.

Summary

A case of acute leukaemia occurring in a male child aged two years is described. An unusual and interesting feature is the loss of one eye, which, beginning with peri-orbital ecchymosis, progressed over a period of twelve days to spontaneous extrusion. The differential diagnosis is discussed.

I should like to thank Professor N. B. Capon, Professor of Child Health, Mr. A. J. McCann, Visiting Ophthalmic Surgeon, and Dr. A. G. Hall, Pathologist, for much helpful criticism and advice, and Dr. W. E. Crosbie, Medical Superintendent, for permission to publish this paper.

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A CASE OF PYOSALPINX IN A NEWBORN INFANT

BY

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Infections of the uterine adnexa are extremely uncommon in the neonatal period. Raso (1942) has reported one case of salpingitis in the newborn infant. He was unable to find a similar case in the literature at that time. His patient had suffered from severe umbilical sepsis and died from peritonitis on the eleventh day after birth. At necropsy there was marked umbilical sepsis, peritonitis, and early bilateral bronchopneumonia in addition to hepato-splenomegaly, which the author attributed to syphilis. The left Fallopian tube was found to be enlarged to two or three times the normal size in its middle third. There was a fibrino-purulent exudate in this region. On histological examination the surface epithelium of the mucous membrane was found to be relatively intact, but the corium was the site of an acute inflammatory reaction. The regional lymphatics were also full of pus. The serous coat was involved in the general peritonitis. Streptococci were found in the affected area. The opposite tube and uterus were quite healthy. The author suggested that the sepsis had spread to the peritoneum from the umbilical area and thence to the left tube via the lymphatics. He contrasts this pathogenesis with that of gonococcal salpingitis derived from an endometritis, and considers it resembles more closely septic lymphangitis of the Fallopian tubes in adults. Dunham (1933), in a review of sepsis in the newborn, reported several cases of peritonitis but in no instance were the tubes or ovaries involved. Martz and Foote (1938) have reviewed the literature concerning pyosalpinx in women. The earliest age of onset quoted therein is fifteen years. Dodek (1933) reported one case of a ruptured ovarian cyst in a newborn infant and considers the differential diagnosis.

The following case is one of neonatal pyosalpinx. It differs from the case reported by Raso (1942) in its pathogenesis but a streptococcus was isolated in this case also. Not only is the condition rare at this period, but, as will be shown, it can be a difficult one to diagnose.

Case Report

Baby McI., born on July 21, 1948, was the second child of a mother aged 28 years. The first child had been born spontaneously and is alive and well. When carrying this second child the mother had suffered from infective hepatitis. Following an antepartum haemorrhage she went into labour twelve weeks before term, and was spontaneously delivered of a small (3 lb. 9 oz.) limp and oedematous infant.

There was evidence of inhalation of amniotic fluid and prophylactic penicillin was given for a few days. Oedema was progressive and the fluid intake was accordingly reduced. No meconium was passed during the first thirty-six hours of life, but, after rectal examination late on the second day, frequent and bulky meconium stools followed, including, on the third day, what appeared to be a cast of the bowel.

This relieved some abdominal distension which had been present, and on the tenth day the abdomen appeared normal and the infant was free from oedema, with the resultant loss of eleven ounces in weight since birth (19·3 per cent. fall).

Until two weeks old the baby had shown evidence of distressed respiration when removed from an atmosphere of continuous oxygen, but following that time oxygen was only given during or after feeding. The feeds consisted of expressed breast milk with additional amino acids.

On the twenty-sixth day the baby, which had shown some improvement and had begun to gain weight, was observed to have a small bead of yellow pus within the vulva in a position which occasioned some doubt as to whether it were of urethral or vaginal origin. A swab was taken and produced a mixed growth of B. coli, B. proteus, and a haemolytic streptococcus not of group A. A clear specimen of urine was obtained by catheterization and showed no pus cells on microscopic examination and grew a few colonies only of B. coli and enterococci. No further pus appeared but a short, forty-eight-hour, course of sulphadiazine was given.

The baby's abdomen was again noted to be distended on the twenty-ninth day, and on palpation of the abdomen a large mass was felt in the right loin. The tumour was firm and fixed. It extended to 5·0 cm. below the costal margin, and it had a rounded lower pole. Above, it merged into the liver and could not be defined, and a rough estimation of 6·0 cm. in length by 4·5 cm. in breadth was made. Posteriorly the right loin was bulging and on percussion anteriorly the note was

tympanitic until it encroached upon liver dulness above.

Liver and spleen appeared normal in size. Some dilatation of veins was visible on the anterior abdominal wall.

Radiological examination showed, on a straight film, slight elevation of the right dome of the diaphragm and a large area of irregular calcification 4·0 × 2·0 cm. in the right side of the abdomen lying approximately between the twelfth rib and a point a little above the iliac crest (fig. 1). It appeared to be too far lateral for kidney and extended below the shadow of the liver. A line of

FIG. 1.—Radiograph of abdomen: antero-posterior view, showing calcified mass below right lobe of liver.

calcification appeared to extend upward almost to the level of the diaphragm. A small opacity was seen lying more medially at the level of the twelfth rib, and one or two doubtful shadows were seen below the left dome of the diaphragm. There was also a shadow in the pelvis to the left of the midline. A lateral radiograph of the abdomen showed the calcification to be lying in a somewhat intermediate position in the posterior half of the abdomen but some distance in front of the spine. The calcification in places appeared to consist of little seeds which did not alter their position when the infant was inverted and were construed as tiny calculi fixed within a tumour mass or in the wall of a cyst. Excretion urography using intramuscular diodone failed to define the urinary tract at all clearly.

A tentative diagnosis of an embryoma in the region of the genital ridge was made and surgical opinion immediately sought.

FIG. 2.—Specimen showing abscess cavity attached to liver. There is great elongation of uterus and vagina. The left tube and ovary are normal.

The following day distension was more marked and the baby's temperature was falling to subnormal level. The bowels were opening normally and the surgeon, after consultation with the radiologist, decided to observe rather than attempt immediate laparotomy. The baby's condition was poor and he could not agree with the provisional diagnosis, feeling it conceivable that the calcification might rather be taking place in a retroperitoneal haemorrhage occasioned by trauma.

During the next forty-eight hours, however, conditions deteriorated steadily. Distension of the abdomen was progressive and a ladder pattern of intestinal peristalsis was marked not only by its prominence on a poor abdominal wall, but by its great activity. Vomiting of bile commenced and became more frequent, and acidotic breathing appeared. Despite this the bowels continued to open two to five times daily and the stools were yellow or brownish yellow, containing no blood.

Surgical intervention was now quite out of the question but a last attempt was made to hydrate the baby and restore the electrolytic balance. Soluble sulphathiazole was given (0·125 g. six-hourly).

On the night before death (the thirty-second day) very obvious gastric peristalsis accompanied the vomiting of bile, and the stools became more frequent and offensive. The following morning the baby was moribund, the respirations were laboured, the chest was full of coarse crepitations, and death ensued before mid-day.

POST-MORTEM REPORT. The body was that of a rather small premature female infant aged five weeks and weighing 3 lb. 4 oz. The abdomen was greatly distended and the skin was taut over the anterior abdominal wall. No congenital abnormalities were found on external examination.

The pleura was clear and glistening and there was no free fluid in the pleural sacs. The lungs were reddish pink in colour and quite well expanded. On section both lower lobes were moderately congested and a small quantity of whitish fluid could be expressed from the cut ends of the intra-pulmonary bronchi. As far as could be judged on macroscopic examination, there was no pneumonia. The pericardium was clear and glistening and there was no free fluid in the pericardial sac. The heart was of normal size and shape; the chambers had a normal appearance, and the endocardium was healthy. Both the foramen ovale and ductus arteriosus were narrowly patent. No congenital abnormalities were present.

The peritoneum was rather dull and there was an extensive fibrinous peritonitis. This fibrinous exudate closely bound the coils of intestine one to the other, but no actual pus was present in the peritoneal cavity. The stomach was rather distended and contained some partly digested food material and mucus. The small bowel was rather dilated, possibly due to a paralytic ileus following on the peritonitis. The coils of intestine were firmly adherent to each other and also to a mass of inflammatory tissue attached to the right lateral abdominal wall. The terminal ileum and the caecum and appendix were closely bound down to the lateral abdominal wall in this region. The ascending colon, transverse colon, and pelvic colon were quite healthy. The rectum showed no change. The liver was of normal size and shape. The capsule was smooth except at its right inferior border where the liver was firmly attached to a mass of tissue lying close to the right lateral abdominal wall. The lower border of the right lobe of the liver was so firmly adherent that it could not be separated from the underlying tissue. On section the liver showed slight fatty change and also a slight infiltration of white matter at its lower border. This was probably a direct extension from the mass of inflammatory tissue. The spleen was three times normal size. The capsule was smooth and on section the organ was rather soft in consistency. The suprarenal glands had a normal appearance and the pancreas appeared to be healthy. The kidneys were small and showed a marked degree of foetal lobulation. The capsule was smooth and stripped easily, and on section a very mild degree of hydronephrosis was present in each kidney. Both ureters were also enlarged to about twice their normal diameter. This was due to mechanical pressure only. The bladder was not affected. After removal of these abdominal organs it was possible to attempt to dissect the mass of tissue lying anterior to the right kidney and firmly attached to the lower border of the liver and the right lateral abdominal wall. In doing so the mass was ruptured and a considerable quantity of thick greenish pus escaped. Specimens of the pus were taken for bacteriological examination. The tissue was then freed from the anterior abdominal wall and it now became obvious that it was continuous with the external genitalia, being connected to the latter by a long hollow muscular tube some 15 cm. in length and ½ cm. in diameter. The upper mass of inflammatory tissue, the muscular tube and the external genitalia were removed en bloc. It was found that a probe could be passed from the vagina along this hollow tube to reach the lower pole of the inflammatory mass, thus accounting for the escape of pus per vaginam on one occasion. The upper inflammatory mass measured 3·5 cm. in length by 2·5 cm. in diameter. It consisted of thin muscular tissue and, after removal of pus, its inner aspect was seen to be lined with innumerable greenish black, small, hard calculi. Further examination showed that the inflammatory mass occupied the position of the right tube and ovary. No ovarian tissue was recognizable; it had been totally destroyed by the inflammatory reaction. The left tube and ovary were perfectly normal.

MICROSCOPICAL REPORT. The right Fallopian tube was the site of a chronic inflammatory process with a coincident acute inflammatory reaction. The mucous membrane had been destroyed and replaced by fibrous tissue. Some necrotic pockets of pus were undergoing calcification and were surrounded by foreign-body giant cells. In the more superficial layer there was a marked infiltration of polymorphonuclear leucocytes.

Liver. The liver cells were healthy and their normal lobular architecture had been preserved. The portal tracts had a normal appearance and the bile ducts were healthy. In one area, however, the capsule was replaced by a mass of acute inflammatory tissue. Without this zone of acute inflammatory

tissue there was a zone of chronic inflammatory tissue and the Fallopian tube was attached to the adjacent liver. From this inflammatory zone there had been a direct extension of the infection along the portal tracts into the immediately adjacent liver tissue, and many lobules and portal tracts had been replaced by acute inflammatory infiltration with formation of small abscesses. The predominant cell in these areas was the polymorphonuclear leucocyte. The deeper portions of the liver had entirely escaped.

Abdominal lymph node. The capsule was normal. The germinal follicles were well developed and had a normal appearance. The sinuses were packed with lymphocytes and there was considerable reticulo-endothelial proliferation. The picture was that of chronic lymphadenitis.

Pancreas, lungs, kidneys and spleen showed no pathological change on histological examination.

BACTERIOLOGICAL REPORT (pus from abdomen). In the direct films were seen numerous pus cells and several Gram-negative bacilli and Gram-positive cocci, shown by culture to be B. coli and enterococci.

SUMMARY. This baby had pyosalpinx of the right Fallopian tube with adhesions to the liver, local abscess formation in the liver, and fibrinous peritonitis.

Discussion

The abscess cavity, uterus and vagina, and external genitalia were removed en bloc at necropsy (fig. 2). Further dissection of this specimen after formol-fixation made the pathogenesis of the condition more obvious. The interior of the vagina and uterus were quite healthy. There was no evidence of endometritis, cervicitis, or vaginitis. The left Fallopian tube and ovary were also quite normal. The right Fallopian tube, however, was greatly distorted. It was bent back upon itself near its uterine end and firmly attached to the posterior uterine wall by numerous adhesions. The tube was dilated and hypertrophied in this region. It contained some thin watery pus, but the mucous membrane appeared to be almost normal. Distally the tube (0·75 cm. from its uterine orifice) opened directly into the abscess cavity, with which there was free communication. Infection had obviously settled down in the distal half of the right tube. This had proceeded to a pyosalpinx, and the large abscess thus formed destroyed all recognizable tissue, including the terminal portion of the tube and the ovary (fig. 3). The infection must have been a low-grade one, and organization proceeded pari passu with inflammatory destruction. This caused the formation of dense adhesions firmly binding down the abscess wall to the lateral abdominal wall and the inferior border of the liver. It may well be that when the infection began the right ovary was not fully descended and thus facilitated the attachment of the tube to the liver and structures in the right upper quadrant of the abdomen.

The great elongation of the uterus (3·5 cm.) and vagina (4·5 cm.) was purely mechanical in origin and caused by the growth of these organs between two fixed points, namely the liver and the vulva. There was no evidence of embryological maldevelopment or infection in either uterus or vagina.

The source of infection is not easily determined. In view of the nature of the pathological and morphological changes, it would seem probable that the infection had commenced in utero. It is interesting to note that the mother had suffered from infective hepatitis during the early months of pregnancy. The organism responsible for the lesion would seem to be a haemolytic streptococcus not belonging to Lancefield's group A. Other organisms

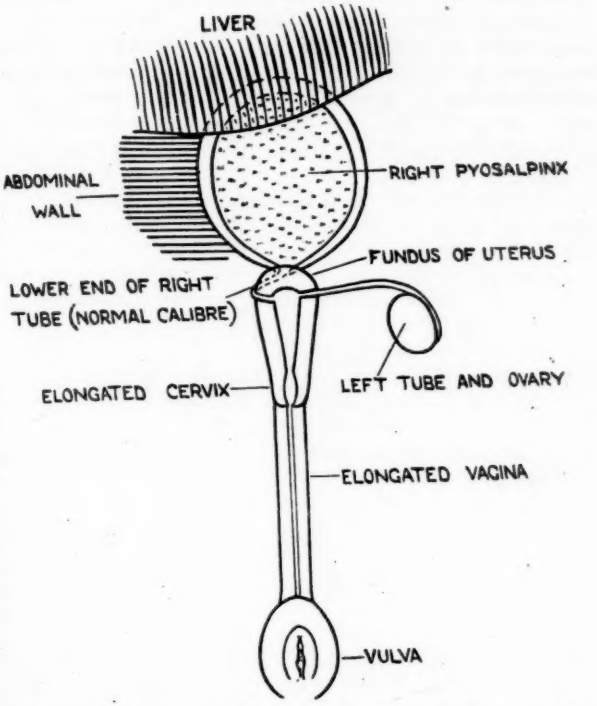

FIG. 3.—Diagrammatic representation of diseased tube and abscess cavity.

isolated from pus during life were probably contaminants from the napkin area. It would seem likely that the infection in this case was blood-borne.

Richmond and Moore (1947) have reported a case of intra-abdominal abscess causing intestinal obstruction in a newborn infant. They postulate the transplacental transmission of the organism concerned. It is interesting to note that in their case also the mother had suffered from jaundice during the fifth month of pregnancy.

The clinical signs presented are readily explicable once the pathology is known. It is regretted that such scant attention was paid to the single bead of pus found within the vulva on the twenty-sixth day. This, it was thought at the time, might be the product of a loculated pyonephrosis which had momentarily discharged some purulent material

into the urinary tract. When the abdominal mass was no longer believed to be of renal origin, no serious attempt was made to explain this purulent discharge, which was regarded as a result of stasis.

Abdominal distension was due initially to the increasing size of the abscess and its adjacent adhesions, but latterly was certainly due to a paralytic ileus with consequent intestinal obstruction, as the peristaltic waves were no longer transmitted onward.

Bowel motions continued since the large bowel was healthy and would consequently evacuate its contents. Veins are always clearly visible on the distended anterior abdominal wall of a small premature infant, but in this case the numerous adhesions involving the liver may have been responsible for an element of portal obstruction. The radiological appearances with apparent spread of calcification to liver and pelvis are now readily understood.

The case was an intriguing clinical and pathological problem and one to be remembered in the differential diagnosis of an intra-abdominal mass in the neonatal period.

We wish to express our thanks to Prof. R. W. B. Ellis for permission to publish this case.

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INFANTILE CORTICAL HYPEROSTOSIS

BY

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Under this title Caffey (1939, 1946; Caffey and Silverman, 1945) described a hitherto unrecognized syndrome that occurs mainly in babies during the first six months of life. All Caffey's cases were seen in the North American continent. This clinical note concerns a case of the syndrome which appears to be the first to have been observed in this country, though Ellis (1938) presented what was possibly a mild example. Other authors who have described cases are Smyth et al. (1946), who reviewed the literature without mentioning Caffey's cases, and Dickson et al. (1947).

According to Caffey the characteristics of the condition are (1) tender swellings deep in the soft tissues, (2) cortical thickenings of the skeleton, (3) onset during the first months of life. The skeletal findings are identical, namely, cortical hyperplasia under proliferating periosteum. Several bones are usually affected, but different patients have had different bones involved. In general it is the mandibles, scapulae, clavicles, ribs, and the tubular bones of the extremities which most frequently show the changes. In the soft tissues there are deep, firm swellings without pitting, warmth, or discoloration. Caffey says that the regional lymph glands are not enlarged. The soft tissue swellings lie over the affected bones, but the bones are more affected radiologically than clinically. Other features described by Caffey are fever, anaemia, pleurisy, and increased erythrocyte sedimentation rate. The course is uneven, with irregular temperature. Some swellings appear as others are disappearing, and even recur in former sites. All the cases recovered after weeks or months of illness. The bony changes persisted longer than those in soft tissue. No cause was discovered. Investigations for bacterial, traumatic, and vitamin deficiency etiology were all negative, and no evidence of virus disease could be discovered.

Case History

I.H., aged 2 months, was admitted to hospital on March 13, 1947. He had had conjunctivitis of the left eye ten days previously, swelling of the left side of the face for one week, and fever for three days; two days before admission his illness was diagnosed as 'pneumonia.' He had had diarrhoea for twenty-four hours, with green motions; he was reluctant to take food but was not vomiting. The birth weight was 7 lb. 4½ oz., the weight on admission 10 lb. 11 oz.

Examination showed him to be well nourished, with no dehydration. There was a rapid, grunting respiration, and a few coarse, moist sounds in the right pulmonary mid-zone. He had generalized swelling of the left side of the face, which was tender. There was some enlargement of the tonsillar lymph glands, the left more than the right. Otherwise nothing abnormal was noted. He was given penicillin, 50,000 units, three-hourly by mouth, and sulphadiazine 0·25 g. six-hourly.

March 14, 1947. The temperature continued at 103°-104° F. Penicillin, 5,000 units four-hourly, was given intramuscularly, and sulphadiazine was also continued four-hourly.

March 18. Chemotherapy was discontinued on account of lack of effect. By next day the temperature had dropped to 101° F. The condition was otherwise unaltered.

March 24. The patient was generally less well and very pale. The blood count showed marked anaemia (see table). The Mantoux test was negative. A firm swelling was noticed in the middle of the shaft of the left humerus. A radiograph was reported as showing well marked periostitis of the left humerus and early periosteal elevation of the other long bones.

April 1. There was marked tender swelling of the whole of the right tibia, and the patient was perspiring continuously. He was still febrile, the temperature remaining between 100° and 101° F.

April 6. The right mandible was now involved, and there were shotty glands on both sides of the neck. Two days later both radii were involved, and both tibiae swollen. There was no further change in the condition of the left humerus.

April 17. The temperature was somewhat higher, between 101° and 102° F. The patient was paler, and the blood count showed less than 2,000,000 red cells per c.mm. of blood. The next day he was transfused with 200 ml. of Group O blood. Two days later a biopsy was performed on

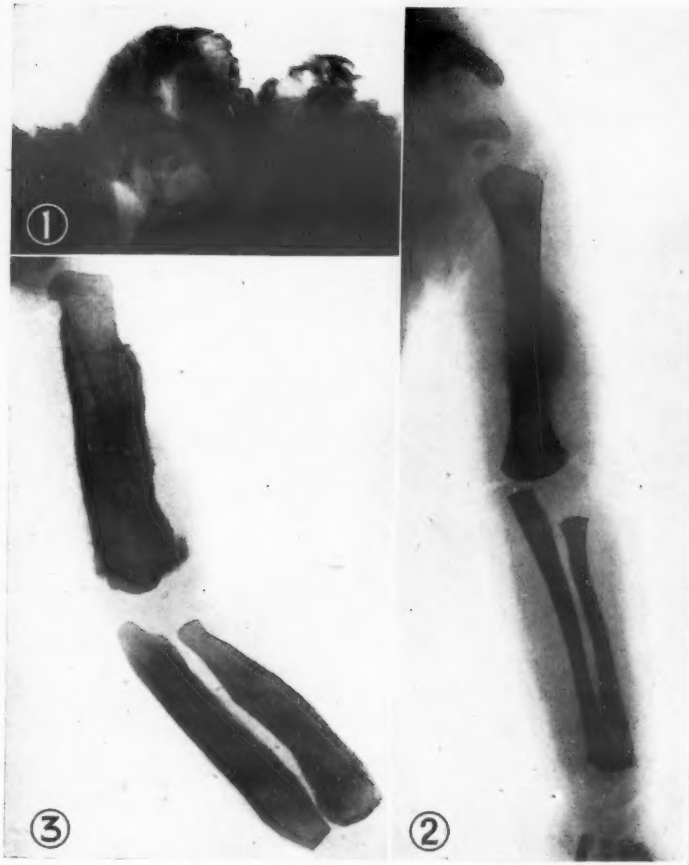
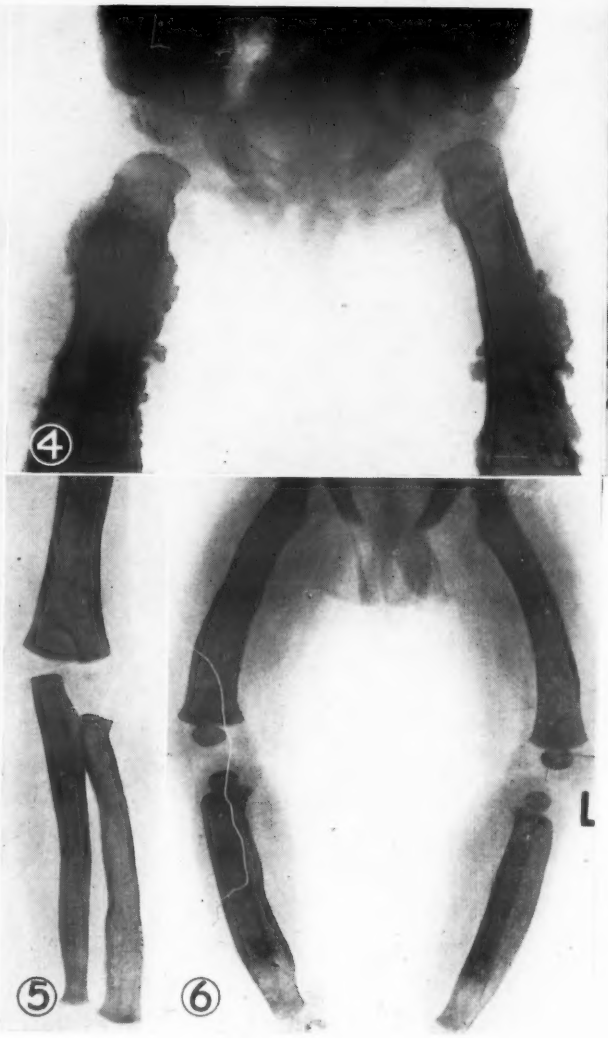


FIG. 1.—Lower jaw about ten weeks after onset of disease, showing massive new bone formation. (July 1, 1947.)

FIG. 2.—Left humerus, radius, and ulna at clinical onset of bone swellings (March 26, 1947). The humerus already shows marked change, while there is periosteal elevation on radius and ulna. Other long bones showed similar periosteal change at this stage.



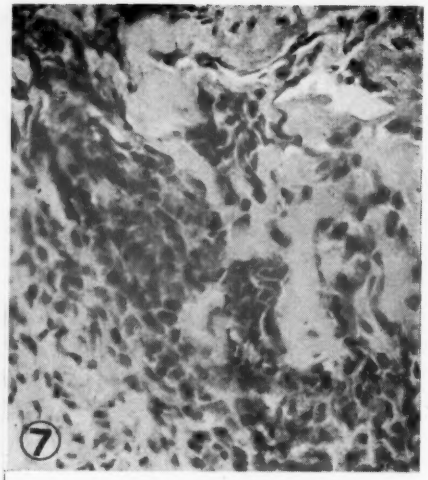


FIG. 3.—The left radius and ulna at the height of the condition, about eight weeks after onset (May 12, 1947).

FIG. 4.—Both femora at the same date. Note the focal and linear formation of new periosteal bone (May 12, 1947).

FIG. 5.—Bones of the left arm showing almost complete healing and remoulding, five months after onset of the disease (Sept. 1, 1947).

FIG. 6.—Leg bones at the same time.

FIG. 7.—Photomicrograph of periosteum of tibia, showing numerous osteoblasts five to seven layers deep (normal one or two layers).

the right tibia and the gland of the neck was aspirated. A postoperative blood transfusion of 200 ml. Group O blood was given.

April 28. All the long bones were increasingly involved and the overlying soft tissues were tense. For details of the blood count see the table.

May 10. The temperature had now dropped to 99°-100° F., and the general condition had improved, the soft tissues of the forearm and calf being rather less tense. Three days later there was considerable enlargement of the inguinal axillary and cervical lymph glands and also of the supratrochlear glands.

May 22. The condition was improving, the temperature being now between 98° and 100° F.

June 14. There was rapid gain of weight following increase of carbohydrate (dextri-maltose) in the diet. The weight had previously been increasing slowly after remaining approximately steady for the first five weeks of illness.

June 26. The gland swellings had now disappeared. In general appearance the patient had a heavy square jaw, and limbs somewhat thicker than average. Otherwise he was well, with a temperature between 98° and 99° F. The child was discharged from hospital, and progress was satisfactory. He was last seen in April, 1948, one year after the beginning of the illness. At this time he was aged 15 months, walking, and well developed. Radiographs of the bones show marked remoulding, the shapes being almost normal although the cortices are rather thin and the bones considerably broader than the average for his age. There is some ossification across the tibio-fibular interosseous membrane at two points.

RADIOGRAPHS. Serial radiographs showed first a diffuse periosteal reaction in the left humerus and left mandible, noticed simultaneously when already well developed. Thereafter all the long bones became involved to a greater or less degree. The first incident was raising of the periosteum, then irregular bone formation, the bone being laid down in discrete, circular patches as though along a vessel, and finally coalescing into massive bony hypertrophy involving the whole of the diaphysis. The ribs and pelvis were also involved. The skull and the small bones of the hands and feet escaped. Ultimately there was moulding into normal-looking bones of good shape but broader than average for the baby's age and size. The cortices were rather thin (see illustrations).

Comment

It will be seen that this case conforms closely to the clinical picture described by Caffey. The patient's age, and the mode of onset are similar to those of most of Caffey's patients. The fever, anaemia, and bone and soft tissue changes all conform to his description.

Certain points emerge where there were differences in the clinical picture, or where it is possible to elaborate on Caffey's observations. On the whole the fever ran a very regular course in that the

TABLE

INVESTIGATIONS ON PATIENT

Blood Counts

Date	R.B.C.	Hb. (%)	Colour index	W.B.C.	P. (%)	L. (%)	M.	B.	E.
24.3.47	2,520,000	46	0·9	27,650	70	23	5	0	1
17.4.47	1,990,000	34	0·8	13,150	56	38	4	0	2
21.4.47		66	Some anisocytosis and polychromasia (following transfusion)						
25.4.47		63	"	"	"	"	"		
29.4.47	4,140,000	64	0·8	8,050	48	41	3	0	7
13.5.47	3,440,000	54	0·8	12,200	58	33	7	0	2
22.5.47	3,420,000	66	1·0	19,800	40	56	2	0	0
			2 lymphoblasts seen						
4.6.47	3,740,000	72	1·0	11,400	54	42	1	0	3
24.6.47	4,890,000	71	0·74						
28.7.47		80	Moderate anisocytosis and polychromasia						

Wassermann and Kahn reactions negative

Serum	Ca (mg. %)	P. (%)	Alkali serum phosphatase	
28.4.47	10·0	5·6	14.4.47	86 King and Armstrong units
22.5.47	8·3	4·8	22.5.47	96 " " "

Urine was sterile, with no abnormal constituents.
Cultures of glands and bone marrow, sterile.
Blood urea 28 mg. per 100 ml. Blood sugar 88 mg. per 100 ml.

temperature was high at the outset and during the course of three months settled down to normal levels. The difference between morning and evening temperatures was seldom more than 1° F. Chemotherapy had no effect on the temperature chart. The baby's weight remained approximately stationary during the higher temperatures of the first three weeks, and thereafter gained steadily with the exception of a sudden increase when additional dextrimaltose was included in June. The calorie value of the food was never below 60 per lb. of body weight per twenty-four hours, and was gradually raised to over 70 per lb. The child seemed to require food of this high calorie value, and after the first few weeks was hungry and eager for his feeds.

The anaemia became marked, and transfusion was required on two occasions, the second being after the biopsy of bone. The blood loss during this operation was slight.

The swelling of the soft tissues in the neighbourhood of the affected bones was marked. The calf muscles especially appeared indurated and tender, and the baby cried when the limbs were moved. At other times he lay quietly and not, apparently, in pain. The tenderness of the calf muscles persisted long after all discomfort had disappeared from other parts of the body.

All the ribs of the patient were markedly involved except the twelfth pair, which remained quite unaffected. In contrast to Caffey's cases with similar rib changes, no evidence of pleurisy was found.

Generalized enlargement of the lymph glands was observed after the illness had been in progress for about two months. Enlargement of the cervical lymph glands was present when the baby was first seen, and persisted for about three months. All the glands appeared to subside together. This lymph-gland enlargement was in direct contrast to Caffey's observations. A biopsy of the glands was performed, but no specific changes could be found microscopically.

The pathological investigations may be summarized as follows: There was marked secondary anaemia which had to be treated by transfusion. The red cell count fell at one time below the 2,000,000 per c.mm. of blood. This was severe leucocytosis with polymorphonuclear predominance, but there was also an absolute increase in lymphocytes. This white-cell reaction subsided after transfusion but recurred, though to a lesser extent, a month later, and finally disappeared leaving a normal count for the age.

Syphilis and tuberculosis were excluded from the diagnosis. The blood chemistry was within normal limits except for the blood phosphatase, which was very high and remained so during the period of active bone change.

Diagnosis

The first diagnosis made was periostitis. Syphilis was considered likely but was excluded serologically. Scurvy was another possibility, but it was known that the baby had had adequate vitamin C before coming to hospital, and in any case he had had routine amounts in hospital before the bony swellings were noticed. The condition developed and progressed during the time when vitamin C was being administered. The final exclusion of scurvy was made by examination of biopsy material from the tibia.

There had been no trauma, and neoplasm was, from the nature of the swellings and the distribution, also improbable. Infective periostitis of non-suppurative type was a possibility, but no evidence of any infection could be found, and biopsy again showed that the swellings were not inflammatory.

The etiology of this curious condition is not yet known, but it would appear that some stimulus causes the periosteum of the cartilage bones to take on abnormal activity. It proliferates rapidly and lays down bone irregularly, finally consolidating into firm dense homogeneous bone and becoming moulded to the normal shape of the bone. The child is left with bones which are larger and, as it were, considerably ' older ' than their chronological age.

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PROGRESSIVE MYOSITIS OSSIFICANS : REPORT OF A CASE

BY

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This rare disease of the locomotor system occurs during the period of growth, and insidiously but inevitably brings about immobilization. It is characterized by the appearance of bone in muscles, tendons, fasciae, and aponeuroses, and by the occurrence of exacerbations and remissions in the course of the disease, and of congenital bony anomalies.

According to Batten (1910), the earliest case on record was reported by Frieke in 1740, and the same author mentions that a complete account was given by Robert, Bishop of Cork, and the Reverend Dean Copping, in 1741, of a boy who showed the first signs of the disease at eighteen and died at the age of sixty-one.

Koontz (1927) mentions that Patin in 1692 wrote of a woman 'who became as hard as wood all over', that the condition was given its present name by Von Dusch in 1868, and that Munchmeyer wrote the first description in 1869. He also states that Helferich in 1879 first noted the association with microdactyly. Koontz mentions some theories of causation, viz. retention of calcium, congenital predisposition towards ossification of intramuscular connective tissue, fascia, and aponeurosis, extravasation of blood into tissue, inflammatory process of intermuscular connective tissue, and disturbances of embryonic development.

Rolleston (1901) believes the condition to be a developmental disease of the mesoblast. He mentions similar ideas as to the cause. It is suggested that in myositis ossificans progressiva the process is a metaplasia of fibrous tissue to cartilage and bone. The disease is, in a sense, misnamed, as the whole pathological process is enacted in and around interstitial connective tissue. In essentials the disease consists of a gradually progressing ossification in this tissue, during the process of which muscle fibres become atrophied and compressed and disappear. In some instances the process may not go so far, for example in calcinosis interstitialis multiplex, where the interstitial connective tissue is the site of deposition of calcium salts. These two closely allied conditions are due to a primary disturbance of development of connective tissue on which is superimposed a disorder of calcium metabolism of unknown origin, permitting in the one case the development of hard, bony masses and in the other of calcium deposits in similar situations.

Koontz (1927) mentions that Rosenstirn reports three instances in which heredity appeared to be a factor. In one instance the grandfather, father, and three sons all had microdactyly and a tendency to haemorrhage.

No treatment is known which will alter or arrest the course of the disease, although the coincidence of treatment with a remission has led to reports of apparent cure. For example Frölich (1926), who noted that fractures in diabetics did not heal readily, thought that ketosis might influence the condition favourably. A patient aged two years six months was placed on a ketogenic diet for eighteen months. No more calcareous areas developed and, of the ones already present, some disappeared and others diminished greatly in size. Van Creveld and Soeters (1941) mention several therapeutic agents which have been employed with disappointing results: for example beryllium carbonate (to form an insoluble phosphate in the intestine), ketogenic diet, sodium citrate (on the basis of the good results obtained in calcinosis interstitialis), parathyroid (used without effect in their reported case), vitamins B_1 and E, disodium hydrogen phosphate (favourable results in calcinosis interstitialis), and a low calcium diet. Deep x-ray therapy and surgical removal of bone have produced no beneficial result. Clinical features of the disease are 'accident proneness', a tendency to tissue haemorrhage, with bone dystrophies in 70 per cent. of cases (Uehlinger, 1936), and the occurrence of remissions and exacerbations. The disease tends to be more common in males than in females in the ratio of four to one. It commonly affects the muscles of the back, with fixation of the scapula to the thorax. The neck is fixed and bent to one side. Arm movements are limited or impossible. It gradually affects the masseters and temporals and even the ocular muscles. Certain groups escape, viz. those of facial expression, platysma, tongue, deglutition, larynx, diaphragm, heart, perineum, genital apparatus, and sphincters. The diagnosis is made on a history of injury, followed by bruising and the appearance of muscle masses, in association with skeletal abnormalities in young children.

Mair (1932), in a very full discussion of the disease, mentions that torticollis may be simulated at first, and also rheumatic infection. In infancy cephalhaematoma and sterno-mastoid tumour may be simulated. He notes that in the early stages the diagnosis must be made from myositis fibrosa,

which has a similar mode of spread but occurs later in life, attacks the lower limbs first, and is associated with pain; from dermatomyositis, in which involvement of the muscles, skin, and subcutaneous tissues occurs simultaneously and progresses rapidly; from polymyositis haemorrhagica, in which cardiac phenomena are rarely absent and haemorrhage with fever is always present; and from calcinosis interstitialis multiplex ossificans (progressiva et regressiva), in which the lesions are hard, but in a considerable number of cases nodules ulcerate through the skin and discharge their chalky contents. Ryan (1945) has reported, however, a case of myositis ossificans progressiva in which ulceration occurred in the thigh. Congenital abnormalities are generally absent, and in calcinosis interstitialis tendons and fasciae are never attacked. Mair also states that microdactyly is an important but not an infallible help in diagnosis. Mair notes that in the late stages the diagnosis must be made from multiple exostosis, in which there is always a definite point of attachment to the bony skeleton whereas in myositis ossificans progressiva bony masses appear loose in the muscles. The prognosis is grave, and death may be due to intercurrent tuberculosis or pneumonia. If the disease comes on in infancy children seldom live beyond the age of fifteen years.

Case Report

The patient is a female child aged three years, who, in October, 1947, fell and injured the back of her head. About a week after this she was seen by her doctor, who found a hard, painless, non-tender swelling over the occiput. It was an ovoid mass about 1 by 1½ inches which pitted slightly on pressure. There were no other symptoms or signs and the mass softened, became dispersed, and disappeared altogether in three weeks. She was kept under careful observation during this period and no rise of temperature or pulse rate was noted. The child was seen again three weeks later as her parents had noticed a swelling in her neck. It was said that she had received a very slight knock on the back of her head fourteen days previously, which was followed in a few days by this swelling. On examination a hard mass was noticed on the back of the neck to the right of the mid-line and extending from the base of the skull to the level of the seventh cervical vertebra. She was admitted into hospital at this time, on Nov. 10, 1947.

She was the second of two children and had been born by normal delivery at full term, the birth weight being 6 lb. 7 oz. No abnormality was noted at birth. Her mother developed a breast abscess, and the infant was fed on diluted cow's milk with added halibut liver oil and vitamin C. She was vaccinated in early life and immunized against diphtheria, both without abnormal reactions. Development was normal, with teething commencing at nine months. She sat up unsupported at nine months, and walked at the age of thirteen months. She had whooping-cough at the age of six weeks and ulcerative stomatitis at the age of two years. At ten months she had a fractured cervical spine which was treated by immobilization. It was said that although she walked normally, she appeared to fall easily.

FAMILY HISTORY. Her mother had an uneventful pregnancy and had always been healthy. Her father had always been healthy and there was no history of abnormality on either side. The first child, a normal boy, had died following an operation for acute appendicitis.

CLINICAL EXAMINATION. The child was of normal height but appeared pale and fragile and apprehensive. There was a mass on the back of the neck, limited by the mid-line, with some redness of the overlying skin, and a small healed abrasion in the right occipital region. The sclerotics appeared more blue than normal. Muscle tone was poor. The great toes were shorter than normal, apparently consisting of one phalanx only, and associated with hallux valgus. There was similar shortening of the thumbs, and the little fingers of both hands were curved. The central nervous system was normal. No abnormality was found in the cardiovascular system nor in the respiratory system. There was no palpable mass in the abdomen. The only other clinical abnormality detected was a mild patchy glossitis. During her stay in hospital she slipped and sustained a very mild blow on her forehead. A bruise developed rapidly. There was no other evidence of bleeding and Hess' capillary resistance test was negative.

INVESTIGATIONS. Haemoglobin was 76 per cent.; the red cell count 4,300,000 per c.mm. of blood; the differential count: neutrophils 40 per cent., lymphocytes 55 per cent., monocytes 3 per cent., basophils 1 per cent., eosinophils 1 per cent. The bleeding time was 3 minutes 15 seconds, and the coagulation time 6 minutes 45 seconds. Urine examination showed a very faint cloud of albumin, with numerous pus cells and motile bacilli. A coliform organism was cultured. Estimation of creatine in the urine showed creatine (as creatinine) 4 mg. (normal 0 to 15 mg.), and preformed creatinine 0·65 mg. (normal 0·5 to 1 g.). Calcium balance estimations performed on the low calcium diet suggested by Abrahams and Widdowson (1940) were inconclusive. During her stay in hospital she had pyrexia varying from 99·4 to 100·5° F. which was attributed to the urinary infection and which responded to treatment with sulphathiazole and potassium citrate.

A series of radiographs were taken, with the following findings. The chest showed no abnormality. The hand showed a small and broad first metacarpal and middle phalanx of the little finger, and one phalanx only in the thumb. It also showed the curving of the little finger (fig. 1). The foot showed a hallux valgus deformity, and a short and broad first metatarsal, with a deformity of the distal end of this bone. The femur showed a broad neck (fig. 5). The skull had an irregular bony mass below the occiput (fig. 4). All the radiographs of

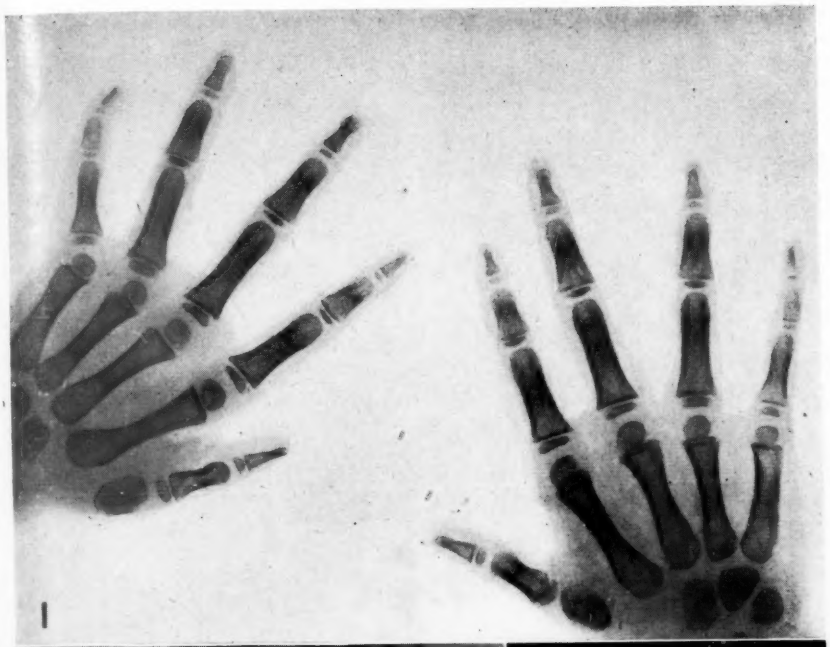

FIG. 1. Radiograph of the hands showing microdactyly of the thumb, apparently due to the absence of one phalanx and a deformed first metacarpal, and terminal incurving of the little finger.

FIG. 2. Photograph showing the child's posture when examined in December, 1947.

FIG. 3. Photograph showing the child's present posture, demonstrating also the site of three bony masses.

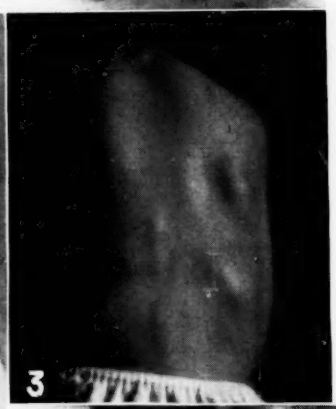

FIG. 4. Radiograph of the occipital and upper cervical regions demonstrating an irregularly shaped bony mass.

FIG. 5. Radiograph of the femora showing the broad femoral neck.

the skeleton showed generalized osteoporosis, and also exostosis at the upper end of the right humerus.

TREATMENT. The patient was treated with iron, vitamins, and sodium citrate.

FURTHER PROGRESS. During her stay in hospital the muscle mass which first appeared in the right trapezius became less and in about two weeks had become flattened and indurated. No other muscle involvement occurred at this time. She was discharged from hospital on Nov. 27, 1947.

On Dec. 11, 1947, rigidity of the right trapezius was noted. The muscles of the spine on the right side felt rigid with two prominent masses (fig. 2), and the whole chest wall posteriorly was hard and unyielding on palpation. She was unable to bend her spine. There was a new mass in the latissimus dorsi in the posterior axillary line. Radiographs of the neck showed increasing density of the muscle shadow.

On Jan. 1, 1948, flattening and contraction of the muscle masses was noticed, with increasing induration, and also thickening and induration of the right deltoid muscle. No mass had been previously observed in this muscle.

On Jan. 20, 1948, a mass was noticed in the right biceps with resulting immobilization of the right elbow at a right angle.

By April 7 there was diffuse thickening of the left rectus abdominis and external oblique muscle with marked induration along the centre of the muscle and near its insertion into the pubis. There were also areas of induration in the abdominal wall near the left costal margin and above the right anterior superior iliac spine.

By Aug. 20 there was curvature of the spine (a dorsal kyphosis) with the head fixed, thickening and rigidity of the left sterno-mastoid, and an indurated swelling below the jaw. The range of movement in the previously fixed right elbow was increased, extension being almost complete but flexion being prevented by a rigid and hard right triceps. The whole of the left rectus abdominis was hard and rigid. There was no evidence of disease in the muscles of the lower limbs. There was thickening and hardening of the masseters with increasing difficulty in opening the mouth. She was able to feed herself with encouragement from her parents. Fig. 3 shows the child's present posture.

Comment

This case shows the common onset in the muscles of the neck with apparent resolution leaving a rigid and considerably smaller mass. Bone which was present in the radiograph (fig. 4) on March 31, 1948, was not shown in a film taken in October, 1947.

Remissions and exacerbations which have been described in this disease are demonstrated, and also the rapid progress and resolution of muscle swellings described by Garrod (1907). The case also shows the association with trauma and the tendency to bruising with almost negligible trauma, although bleeding time was normal and capillary fragility could not be demonstrated. Another feature was the incidence of falls, although it is possible that no comment would have been made on this point except for the consequent bruising. Microdactyly was present in the thumbs and great toes, with hallux valgus deformity in the latter. Radiographs showed bone dystrophies in other bones, viz. the first metatarsal and first metacarpal, the middle phalanx of the little fingers, and apparently the neck of the femur.

Two types of muscle involvement were noticed; one in which there was a dramatic onset of a large mass which resolved over a period of three weeks, and the other in which there was an insidious progress of muscle induration without an apparent antecedent muscle mass. This was noticed particularly in the right triceps and the right deltoid.

In this case the right side of the body had become considerably involved before there was any evidence of the disease on the left side.

Summary

A case of progressive myositis ossificans is reported in a girl of three years, with notes on theories of etiology, clinical features, and differential diagnosis; and mention is made of the numerous but disappointing varieties of treatment.

My thanks are due to Dr. D. Glanville Evans for his careful notes and to Dr. Gerald Evans and Mr. Goronwy Thomas for helpful criticism.

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FAMILIAL INCIDENCE OF CONGENITAL ABNORMALITIES OF THE ANUS AND RECTUM

BY

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Congenital abnormalities of the anus and rectum are among the rarer congenital anomalies, the incidence being variously given as one in five thousand to one in ten thousand live births (Dmytryk, 1945). Murphy (1947) in Philadelphia in his study of 890 dead children with diagnoses of gross congenital malformations and consequent assessment of their families with an addition of forty-five cases, reports ten cases. Under the care of University College Hospital in the past twenty years there have been 28,443 deliveries, and four cases of anomalies of the anus and rectum have been recorded. Feggetter (1939) records uniovular twins with imperforate anus and notes a twinning tendency in the family, but records no further instance of anal anomaly.

Case History

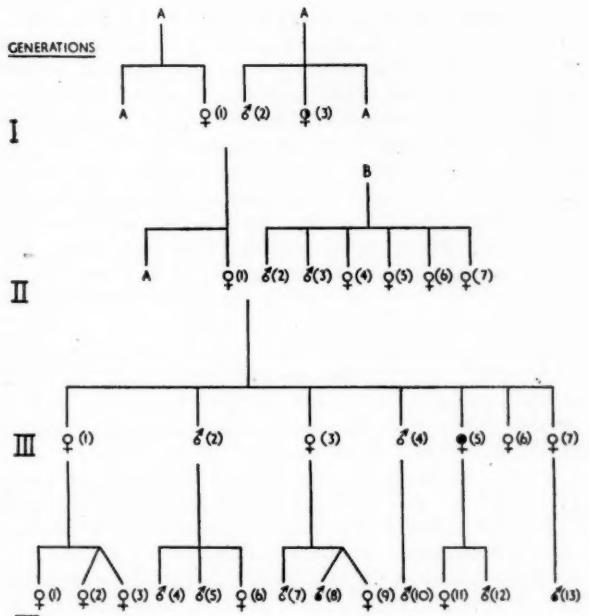
The baby, the first-born and a boy, was delivered by forceps extraction for delay in the second stage of labour, and weighed 7 lb. 3½ oz.

There had been no maternal illnesses during pregnancy. The mother was aged 28, her Wassermann reaction was negative and her Rh factor positive. Her haemoglobin was 60 per cent. There had been no irradiation of either parent.

The infant began to gain weight from birth, and by the fifth day had increased by 8½ oz. Pitting oedema was observed at the knees for which no cause was found. The urine was normal, and serum proteins were 6·8 g. per 100 ml. of blood, with albumin 4·2 g. Blood urea was 24 mg., and plasma chlorides 575 mg. per 100 ml. Urine and meconium had been passed normally.

On the eighth day some abdominal distension was noted, but no ascites was detected and the oedema disappeared. He was taking well from the breast and a few curds were seen in the motions, which were rather frequent but not regarded as abnormal. His weight was now 17½ oz. above his birth weight. His haemoglobin was 132 per cent., with red cells 6,500,000 per c.mm. of blood, white cells 16,600 per c.mm., neutrophils 39 per cent.

On the 9th day there was marked distension of the abdomen and visible peristalsis of the large bowel. An attempt was made to pass a finger up the anal canal, but an obstruction was encountered at a depth of about half an inch. A rectal thermometer



O = apparently normal cases. ◑ = doubtful cases. ● = proved cases. A signifies a Russian family, of which the details are not known. The other family is English.

The generations are given as I, II, III, and IV. Members of the family are referred to by their generation, and consecutive numbers are given in parenthesis.

I. 1-3: Dead—potential ages unknown.
II. 1: fifth child, aged 70.
II. 2: dead, potential age 70.
II. 3: aged 58, alive.
II. 4: „ 56, „
II. 5: „ 54, „
II. 6: „ 52, „
II. 7: dead, potential age 49.
III. 1: aged 51, alive.
III. 2: „ 48, „
III. 3: „ 43, „
III. 4: „ 41, „
III. 5: „ 37, „
III. 6: „ 31, „
III. 7: „ 28, „
IV. 1: „ 32, „ } twins.
IV. 2: „ 22, „ }
IV. 3: „ 22, „
IV. 4: „ 24, „
IV. 5: „ 20, „
IV. 6: „ 12, „
IV. 7: „ 18, „
IV. 8: „ 12, dead. } twins.
IV. 9: „ 12, alive. }
IV. 10: „ 5, „
IV. 11: „ 12, „
IV. 12: „ 10, „
IV. 13: patient.

There is no consanguinity in any of the unions recorded above.

could likewise not be passed. The baby's general condition was quite good, and faecal matter was still being passed in small quantities, but vomiting had begun. A radiograph showed gross distension of the colon with gas.

Operation was undertaken without anaesthesia. A raphé of skin passing antero-posteriorly divided the anus, but not the anal canal, into two. This raphé was cut and a silver probe was passed through a small opening in the recto-anal membrane, with escape of gas and immediate lessening of the intra-abdominal tension, which had been considerable.

The opening was dilated with gum elastic bougies and in later days with Hegars dilators, until the little finger could be inserted. At first the opening tended to seal itself off with faecal matter, necessitating frequent insertions of a rubber catheter.

After operation the baby's condition was fair, but vomiting continued and intravenous nutrition was required for thirty-six hours. Apart from this and a little mucus in the stool for a few days the baby made an uninterrupted recovery. The stenosis is now judged to be about half an inch deep to the external anal margin, and to be about half an inch long. It corresponds therefore to Type I of Ladd and Gross (1941). A barium meal has not been given, but it appears unlikely that there is any further stricture of import in the rest of the bowel. Radiographs of the pelvis, lumbar and sacral spines, and coccyx have disclosed no abnormality.

After the facts of the baby's illness had been explained to them, the family history was elicited from the parents (see chart). There are no known congenital abnormalities on the father's side, and, so far as can be told, other congenital abnormalities have not occurred.

Comment

Case I (3) is a doubtful case occurring in Russia some seventy years ago. Case III (5) has been interviewed and apparently had a rectovaginal fistula operated upon at the age of six months. She has had no further disability, and she declined examination. Case IV (8) died in a London hospital at the age of five months following measles. Confirmation has been obtained that he had an imperforate anus at birth which was operated upon and was apparently similar in type to this patient's. Case IV (13) is this patient.

COMMENT by Dr. H. Harris, the Galton Laboratory, University College. The occurrence of four cases of such a rare congenital anomaly in a single family group strongly suggests that we are dealing with an inherited trait. The configuration of the pedigree indicates that the anomaly is probably determined by a single gene which is ' conditionally ' dominant but incompletely manifesting. The affected individuals are presumably heterozygous for the gene.

The occurrence of the trait in successive generations and the absence of any consanguineous matings rule out the possibility of simple recessivity. There is no suggestion of sex linkage or sex limitation.

I would like to thank Dr. R. E. Bonham-Carter, under whose care this patient is, and Mr. Merrington of the Surgical Unit for their advice and help with the treatment.

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IDIOPATHIC HYPOPARATHYROIDISM

BY

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Cases of spontaneous hypoparathyroidism, although rare, have been reported frequently in the literature (as by Albright and Ellsworth (1929), Snapper (1934), Campbell (1935), Himsworth and Maizels (1940), Goerner and Samuelson (1934), and Robertson (1941)). The disease is characterized by increased neuromuscular irritability giving rise to tetany, and by a lowered blood calcium and raised blood phosphorus. Cataracts may develop in untreated cases. Generalized convulsions may occur. Although many cases arise in childhood, the disease may occur at any age, and one patient described by Snapper (1934) did not develop symptoms until the age of 76. The diagnosis is established when other factors causing tetany such as alkalosis, any form of rickets, osteomalacia, coeliac disease, and steatorrhoea have been excluded.

Idiopathic hypoparathyroidism has been described by Hunter (1931) in his classical review of calcium and phosphorus metabolism, as being a condition analogous to myxoedema in relation to hypothyroidism. Symptomatically it is found to be identical with hypoparathyroidism following too extensive thyroidectomy which has included removal of the parathyroid glands.

A case of spontaneous hypoparathyroidism, which has now been under observation for over six years, and which has presented some unusual features is now reported and discussed.

Case Report

Sylvia A. developed normally until the age of 7 years, having suffered only from acute intussusception as a baby, and measles and whooping-cough in early childhood. At the age of 7, however, it was noticed that her fingers became rigid on first waking up in the mornings, remaining immovable usually for about fifteen minutes. During the spasms her fingers were flexed at the metacarpo-phalangeal joints and extended at the interphalangeal joints. At first these spasms occurred only occasionally but gradually they became more frequent and of longer duration. During them she remained quite conscious and used to laugh at her hands which apparently gave her no pain.

In 1941, at the age of 8, she developed similar attacks of rigidity of her feet which occurred both at rest and during exercise. During these spasms her feet were held in the position of extreme talipes equino-varus, and she often cried out from the pain in her legs. At this time, also, she began to complain of frontal headaches.

One afternoon in August, 1941, she complained of frontal headache and went to bed. An hour later she was found in bed unconscious with marked pallor and rigidity of all her muscles; there was some froth on her lips and her eyes were open and staring. She recovered in five minutes and fell into a deep sleep. During the next six weeks she had many of these seizures, the number varying between one and five a day. The attacks started without warning, and consisted first of a tonic phase lasting two to five minutes, during which time she was very pale, followed by a clonic period of shorter duration accompanied by opisthotonus, frothing at the mouth, biting of the tongue, and sometimes incontinence of urine; the clonic phase was followed by a period of unconsciousness lasting ten to twenty minutes, after which she would fall into a deep sleep. Between the seizures the spasms of rigidity in her hands and feet continued to occur.

In October, 1941, she was given epanutin gr. ¾ at night, and this appeared to reduce the severity of the seizures though it did not abolish them and had no effect on the spasms in her limbs. She was admitted to Harefield Emergency Hospital under the care of Dr. Lightwood on Nov. 13, 1941. Her parents and brother, aged 10, were alive and well, and there was no family history of epilepsy or other disease.

On examination she was found to be afebrile but drowsy. She could, however, be roused to talk intelligently for her age. Examination of her lungs, heart, and abdomen showed no abnormality. Her pupils were equal and active to light, there was no nystagmus, and her eye movements were normal. There was no papilloedema.

No cranial nerve abnormality was detected and her limbs showed no paresis or anaesthesia, all her reflexes were normal. Blood pressure was 105/70 mm. Hg. Her weight was 51 lb. (normal for age 55 to 60 lb.).

Two spasms of her hands occurred on that day, and during each of them her hands were seen to adopt the typical ' main d'accoucheur ' position. After the spasms were over Trousseau's and Chvostek's signs were found to be positive. Investigations at this time showed the blood calcium to be 5·8 mg.

per 100 ml. of blood and 9·8 mg. blood phosphorus. Carbon dioxide combining power was 50·5 volumes per cent. The urine contained no albumin. Blood urea was 40 mg. per 100 ml. A chest radiograph was clear, and one of the skeleton showed no decalcification (compared with a control) and no bony abnormalities.

Analysis of the stools gave the following figures: total fat 29·6 g. per cent.; neutral fat 1·7 g. per cent.; free fatty acid 4·1 g. per cent.; fatty acid (as soap) 23·8 g. per cent.

The cerebrospinal fluid pressure was 175 mm. of fluid. Queckenstedt's test was normal. There was 20 mg. per 100 c.cm. of protein and 720 mg. per 100 ml. of chlorides. There were 3 lymphocytes per c.mm.

Haemoglobin was 90 per cent. (Haldane), and the blood sedimentation rate 9 mm. in one hour.

In view of these investigations a diagnosis of primary parathyroid tetany was made.

Treatment was started after a week in hospital and consisted first in the administration of calcium lactate, 1 drachm three times a day; but this produced no alteration in her tetany or serum calcium. On Nov. 18, therefore, this treatment was discontinued and vitamin D therapy was started. An initial daily dose of 18,000 I.U. of vitamin D_2 (calciferol) was employed for one week but produced no effect on her symptoms or blood chemistry, nor did 36,000 I.U. daily for a similar period. The dose was finally increased to 100,000 I.U. a day, and after two weeks on this treatment both the overt and latent tetany was abolished and her blood calcium rose to 8·9 mg. per 100 ml., whilst the phosphorus fell to 8·2 mg. After a further week her blood calcium had risen to 9·8 mg. per 100 ml.

Daily estimations over the next month showed little alteration in the blood calcium, which remained steady between 9·6 and 10·4 mg. per 100 ml., while the blood phosphorus fell to 5·0 mg. She gained 7 lb. in weight during this period and was discharged home on Jan. 18, 1942, free from symptoms, on a maintenance dose of vitamin D, 100,000 I.U. daily.

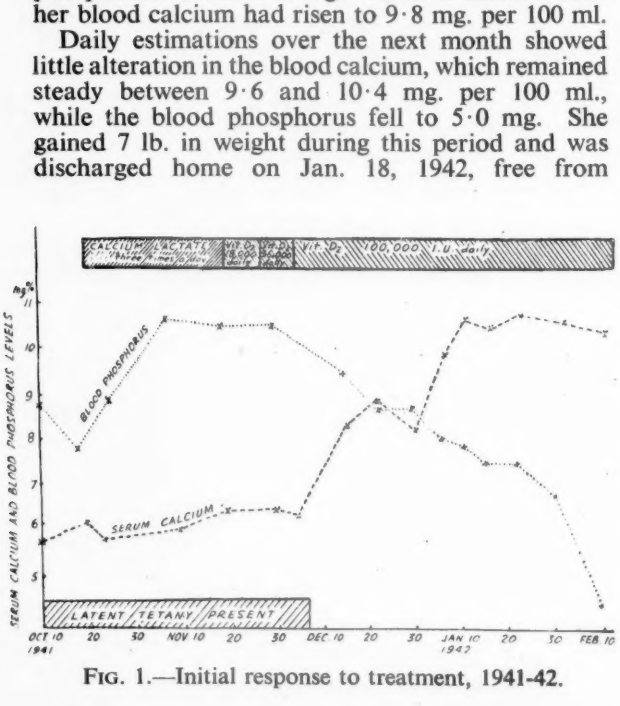
CALCIUM LACTATE
Vit. D2 100,000 I.U. daily
mg%
SERUM CALCIUM AND BLOOD PHOSPHORUS LEVELS
BLOOD PHOSPHORUS
SERUM CALCIUM
LATENT TETANY PRESENT
OCT 10 20 30 NOV 10 20 30 DEC 10 20 30 JAN 10 1942 20 30 FEB 10
1941

FIG. 1.—Initial response to treatment, 1941-42.

During the next two and a half years this dose of vitamin D was continued, and she was observed at the Hospital for Sick Children, Great Ormond Street, as an out-patient. No untoward symptoms occurred until June, 1944, when the vitamin D was discontinued. Two weeks after this she developed frank tetany with convulsions which were relieved by the injection of intravenous calcium gluconate. Blood calcium at this time was 8·2 mg. per 100 ml. The vitamin D was immediately restarted, no further tetany occurred, and her blood calcium returned to normal.

In August, 1944, she developed vomiting, generalized abdominal pain, and constipation, and was admitted to another hospital. She was discharged home after a week, no diagnosis having been made.

After this she continued to have attacks of vomiting, particularly in the mornings, associated with increasing anorexia. She complained of right frontal headaches and became increasingly listless and unco-operative. She was readmitted to Harefield Emergency Hospital in November, 1944, having lost 17 lb. in weight in the previous five months.

Examination now revealed that she was a tall, thin, lethargic girl with sunken eyes and somewhat hirsute skin; she had slight bilateral conjunctivitis. Her lungs were clear. Her pulse was regular at 80 to the minute, and the blood pressure was 115/70 mm. Hg. There was no cardiac enlargement and no murmurs. Her abdomen showed no abnormality. Her central nervous system was normal, and Trousseau's and Chvostek's signs were negative. A chest radiograph was clear. No calcification was seen in a radiograph of the abdomen, and renal outlines appeared normal. A radiograph of the skeleton showed normal calcification (as compared with a control). No bony abnormality was seen.

Serum calcium (thrice repeated) was 15·6 mg. per 100 ml., blood phosphorus 5·4 mg., blood phosphatase 20 (King) units, serum sodium 316 mg., serum potassium 18 mg., and blood chlorides 590 mg.

There was a trace of albumin in the urine, no sugar, and a few granular casts and pus cells. The Addis count was 9 million red cells per twelve-hour specimen. Blood urea was 81 mg. per 100 c.cm. The urea clearance test (thrice repeated) showed 22 per cent. normal function. The specific gravity test showed dilution to specific gravity of 1002, no concentration above 1010. The blood sedimentation rate was 35 mm. in one hour.

Whilst these investigations were being carried out, her maintenance dose of vitamin D was continued, and her marked listlessness, anorexia, frontal headaches, and an irritating continuous dry cough persisted. Over the period from Dec. 28 until Jan. 9, however, her dose of vitamin D was gradually

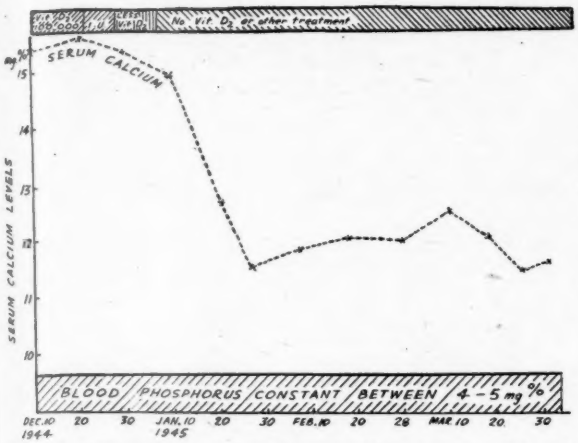

FIG. 2.—Response to withdrawal of treatment, 1944-45.

reduced from 100,000 I.U. to nothing, but on Jan. 12 her blood calcium was still 14·6 mg. per 100 ml. and her blood phosphorus 4·6 mg. During the next three weeks, however, her blood calcium fell steadily till on Jan. 26 it was only 11·4 mg. per 100 ml. and her blood phosphorus 4·8 mg. During this period, also, all her symptoms disappeared and she gained 7 lb. in weight.

She remained in hospital until May, 1945, during which time she was given no vitamin D and her blood calcium remained steady between 11·0 and 12·0 mg. per 100 ml. and her blood phosphorus between 4·2 and 4·8 mg. She gained a further 8 lb. in weight during this time, remaining free from symptoms throughout, except that she had some recurrent staphylococcal furunculosis in both ears which disappeared after treatment with staphylococcus toxoid, and a transient right-sided facial palsy (lower motor-neurone in type) which cleared after eight weeks.

Prior to discharge her urine contained no albumin or casts, and her blood urea was 65 mg. per 100 ml. A urea clearance test still showed her renal function to be only 23 per cent. of normal.

She continued as an out-patient at the Hospital for Sick Children, Great Ormond Street. Satisfactory progress was maintained, and in July, 1945, her blood calcium was still 10·4 mg. per 100 ml.

At the end of August, 1945, however, she developed anorexia, listlessness and vertigo, and on Sept. 11 examination showed serum calcium to be 6·2 mg. per 100 ml., and blood phosphorus 6·3 mg.; latent tetany was present. She was admitted to the Hospital for Sick Children, Great Ormond Street, London.

Renal investigation now showed the urine to have a specific gravity of 1021. There was a trace of albumin but no casts. The Addis count was 6 million red cells in a twenty-four hour specimen. The blood urea was 37 mg. per 100 ml. and urea clearance 50·5 per cent. of normal function. An intravenous pyelogram was within normal limits but concentration was poor in the left kidney.

An electro-encephalogram carried out at this time showed irregular delta-wave activity (abnormal for age) which suggested acquired dysfunction.

Treatment with calciferol, 100,000 units daily, was restarted, and by Oct. 2 her latent tetany had disappeared and she was free from symptoms and gaining weight. She was discharged on a maintenance dose of calciferol, 50,000 units daily.

In November, 1945, her family removed to Birmingham and observation was continued at the Birmingham Children's Hospital under the care of Dr. A. V. Neale. Her maintenance dose of vitamin D was continued and she exhibited no further untoward effects. In January, 1948, she was working as a factory hand and leading a normal life. One further investigation was carried out. In January, 1946, her vitamin D was temporarily withdrawn and in two months she had reverted to a state of hypocalcaemia and latent tetany.

Discussion

There has been considerable discussion in the past concerning the long-term therapy of hypoparathyroidism. Although Campbell (1935) has reported a favourable response in some cases to a high-calcium–low-phosphorus diet together with oral hydrochloric acid, the majority of cases have been treated with vitamin D.

In America, Albright (1939, 1941) has shown good results with A.T.10 (7 dehydro-cholesterol), but in this country Himsworth and Maizels (1940) state that in this condition A.T.10 has little or no advantage over vitamin D_2 (calciferol).

The dangers of vitamin D overdosage have long been recognized and were extensively reviewed by Harris (1932). Hypervitaminosis usually develops after long continued vitamin D therapy due to a cumulative action. This property of cumulative action has been used in this country by Krestin (1945) when giving a single massive dose of vitamin D in the preventive treatment of rickets.

It is, therefore, surprising that after having taken her stabilizing dose of calciferol, 100,000 units daily, from January, 1942, until June, 1944, our patient should revert to hypocalcaemia with frank tetany only two weeks after her vitamin D had been discontinued. It can only be assumed that this dose was the bare maintenance one for her requirements.

But only two months after the same dose of vitamin D had been recommenced she began to develop the classical symptoms of hypervitaminosis D, with lassitude, depression, severe anorexia, constipation, and wasting, with hypercalcaemia and renal damage as described by Harris (1932). There was, however, no radiological evidence of metastatic calcification or increased bony calcification.

Four months elapsed, after the onset of hypercalcaemic symptoms, before she was admitted to our hospital and the vitamin D was discontinued. In less than four weeks after this the blood calcium

had returned to normal and all her symptoms had disappeared. Evidence of renal damage, however, persisted.

Her blood calcium then remained normal with no treatment for eight months. This is in marked contrast to the events following the previous cessation of treatment in June, 1944, when tetany had developed only two weeks after the stoppage of vitamin D therapy.

Parathyroid hypertrophy following renal damage was recognized by MacCallum (1905), and has since been recorded on numerous occasions. The possibility was, therefore, considered that the long period of normal blood calcium in our patient was the result of parathyroid hypertrophy produced by her renal damage. Recent work by Gilmour (1947) has shown that the stimulus for parathyroid hypertrophy in renal damage is most probably hypocalcaemia, itself a secondary consequence of the phosphorus retention and hyperphosphataemia.

Our patient, however, at the time of her renal damage had marked hypercalcaemia, so that it is most unlikely that the renal damage can have stimulated her parathyroid secretion.

The blood calcium and phosphorus levels during the period of renal damage are more probably due to accumulation of vitamin D in considerable quantity during the period of overdosage. When at the end of eight months the supply of vitamin D was exhausted, the patient reverted to her previous state of hypocalcaemia, hyperphosphataemia, and latent tetany. The effects of hypervitaminosis D on her kidneys had also lessened, and her renal function had improved considerably.

When she reverted to a latent tetanic state again at the end of the eight-month period, it was found that her daily requirements of vitamin D had dropped from the previous level of 100,000 I.U. daily to 50,000 I.U. daily, and this dose has been maintained subsequently. One further experiment was tried in January, 1946, when her vitamin D was discontinued; in two months she reverted to hypocalcaemia and latent tetany.

It was apparent, therefore, that in August, 1944, her requirements of vitamin D had lessened for a reason which is not understood but which may have been related to the onset of puberty, and that continuation with her original dosage gave rise to symptoms of hypervitaminosis. When these had subsided it was found that her requirements of vitamin D had decreased to half the original dosage.

It is greatly to be regretted that circumstances prevented us from carrying out calcium and phosphorus balance estimations which might have been of value in the investigation of this case.

Summary

A case of idiopathic hypoparathyroidism is described which responded adequately for two and a half years to a maintenance dose of vitamin D_2, 100,000 units daily. At the end of this time tetany developed after the vitamin D had been discontinued for only two weeks. Two months after the resumption of vitamin D therapy, symptoms of hypervitaminosis D developed with renal damage. After a period of eight months with no vitamin D, during which all symptoms had disappeared and the renal damage had improved, symptoms of tetany reappeared.

The patient has now been restabilized on a dose of vitamin D_2, 50,000 units daily, for over two years. She is well and working. Some possible explanations for this chain of events are suggested.

My thanks are due to Dr. Reginald Lightwood and Dr. A. V. Neale for permission to publish this case, to Dr. Reginald Lightwood for help and encouragement in the preparation of the report, and to Dr. Addenbrooke for the clinical details since November, 1945.

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